Anesthesia and Analgesia

Anesthesia and Analgesia

SCIENTIFIC ARTICLES

REVIEW ARTICLE

CLINICAL REPORTS

Contents

"Let's bring him out, now."

NARCAN® ampuls 0.4mg/ml
naloxone HCl

rapidly reverses respiratory depression of narcotic-supplemented anesthesia

When partial or complete reversal is indicated, NARCAN® will quickly reverse narcotic-induced respiratory depression and help restore consciousness. The result? Your patient may be out of the recovery room and back in his own room sooner. Prompt restoration of the patient's protective reflexes reduces the risk of postanesthetic complications. Moreover, because the dosage of NARCAN can be titrated, the analgesic action of the narcotic can usually be preserved.

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ATIVAN® (LORAZEPAM) IV
INJECTION IM or IV

DESCRIPTION: Ativan® (lorazepam) Injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzo-diazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as w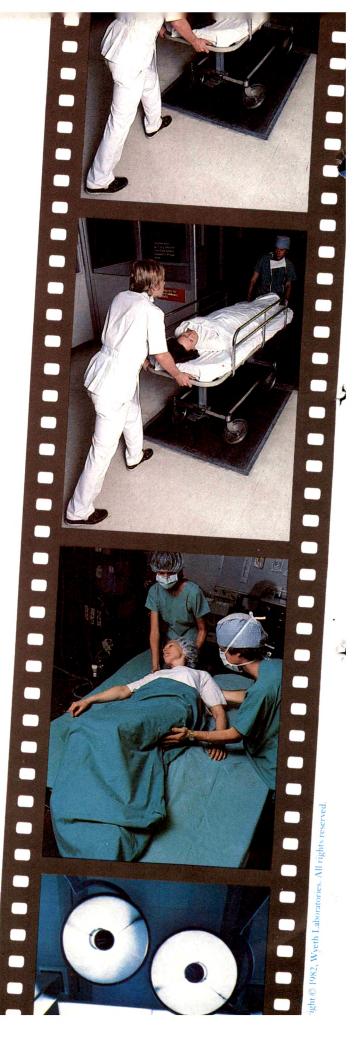ith other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal failure. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately post-injection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure. Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure. EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan® (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.
For IM or IV injection.
Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

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*Although absorption of lidocaine from respiratory mucosa varies widely among individuals, blood concentrations achieved by this route can rise to levels comparable to those reached by similar doses infused intravenously, and in some cases almost as rapidly.[1,2,3]

REFERENCES
1. Bromage P: Concentrations of lidocaine in the blood after intravenous and endotracheal administration. Anaesthesia, 16:461, 1961.
2. Chu S: Plasma concentration of lidocaine after endotracheal spray. Anesth. Analg., 54:438, 1975.
3. Pelton D: Plasma lidocaine concentrations following topical aerosol application to the trachea and bronchi. Canad. Anaesth. Soc. J., 17:250, 1970.

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Xylocaine®
(lidocaine hydrochloride)
4% Sterile Solution

Before prescribing or administering, please consult complete product information, a summary of which follows:

CONTRAINDICATIONS: Lidocaine hydrochloride sterile solution is contraindicated in patients with a known history of hypersensitivity either to local anesthetics of the amide type or to other components of the sterile solution.

PRECAUTIONS: The safety and effectiveness of lidocaine hydrochloride depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for various anesthetic procedures.

The lowest dosage that results in effective anesthesia should be used. Injection of repeated doses of lidocaine hydrochloride may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug or its metabolites. Tolerance varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status. Lidocaine hydrochloride should also be used with caution in patients with severe shock or heart block.

As with all injections of local anesthetics, retrobulbar injection should always be made slowly and with frequent aspirations.

Solutions to which a vasoconstrictor has been added should be used with caution in the presence of diseases which may adversely affect the patient's cardiovascular system. Serious cardiac arrhythmias may occur if preparations containing a vasoconstrictor are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other related agents.

Lidocaine hydrochloride should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine HCl.

Local anesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precaution should be taken to avoid this type of interaction.

The safety of amide local anesthetics in patients with malignant hyperthermia has not been assessed, and therefore, those agents should be used with caution in such patients

Drowsiness following lidocaine hydrochloride injection is usually an early indication of a high blood level of the drug and may occur following inadvertent intravascular administration or rapid absorption of lidocaine.

ADVERSE REACTIONS: Adverse reactions may result from high plasma levels due to excessive dosage, rapid absorption or inadvertent intravascular injection. Such reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system. A small number of reactions may result from hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

CNS reactions are excitatory and/or depressant, and may be characterized by nervousness, dizziness, blurred vision and tremors, followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest. The excitatory reactions may be very brief or may not occur at all, in which case the first manifestations of toxicity may be drowsiness, merging into unconsciousness and respiratory arrest.

Toxic cardiovascular reactions to local anesthetics are usually depressant in nature and are characterized by hypotension, myocardial depression, bradycardia and possibly cardiac arrest.

Treatment of a patient with toxic manifestations consists of assuring and maintaining a patent airway, supporting ventilation with oxygen, and assisted or controlled ventilation (respiration) as required. This usually will be sufficient in the management of most reactions. Should a convulsion persist despite ventilation therapy, small increments of anticonvulsive agents may be given intravenously. Examples of such agents include benzodiazepine (e.g., diazepam), ultrashort acting barbiturates (e.g., thiopental or thiamylal) or a short acting barbiturate (e.g., pentobarbital or secobarbital). Cardiovascular depression may require circulatory assistance with intravenous fluids and/or vasopressors (e.g., ephedrine) as dictated by the clinical situation.

Allergic reactions may occur as a result of sensitivity either to local anesthetics or to other components of the sterile solution. Anaphylactoid type symptomatology and reactions, characterized by cutaneous lesions, urticaria, edema, should be managed by conventional means. The detection of potential sensitivity by skin testing is of limited value.

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LE CHATEAU FRONTENAC, QUEBEC, P.Q.

MAY 22–26, 1982   du 22 au 26 mai, 1982

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SUNDAY	**DIMANCHE**
14 Refresher Courses	14 cours de mise à jour
MONDAY	**LUNDI**
PANEL: Neuro-anaesthesia *Dr. David Trop*	TABLE RONDE: Neuro-anesthésie *Dr. David Trop*
The Residents Competition	*Le concours des résidents*
TUESDAY	**MARDI**
C.A.S. – Royal College Lecturer *Dr. Ronald Melzack* "Current Concept of Pain"	S.C.A. – Conférence annuelle Collège Royal *Dr. Ronald Melzack* "Conception actuelle de la douleur"
WEDNESDAY	**MERCREDI**
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Announcing a new anesthetic concept that provides maximum protection prior to maximum stress

Introducing a
new anesthetic technique:

This new technique—pre-intubation analgesic loading—involves administering enough SUBLIMAZE® (fentanyl) prior to intubation to last generally the length of the procedure. Pre-intubation upfront loading employs the pharmacokinetic properties of SUBLIMAZE® (fentanyl) to best advantage compared with p.r.n. use or administration of the drug incrementally throughout the procedure.

For further information and general guidelines on pre-intubation analgesic loading with SUBLIMAZE® (fentanyl), please contact your Janssen representative or write Janssen Pharmaceutica.

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Sublimaze®
(fentanyl) Injection ©

Protect from light. Store at room temperature.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY
DESCRIPTION
Each ml. contains:

Fentanyl . . . . 50 mcg. (0.05 mg.) as the citrate
Warning: May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0-7.5.

CONTRAINDICATIONS
SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS
AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATION EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.
See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition. Where moderate or high doses are used (above 10 mcg./kg.), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received SUBLIMAZE (fentanyl). It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Drug Dependence—SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure—SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children—The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy—The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS
The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of SUBLIMAZE (fentanyl) are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol) hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol).

When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS
As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with *INAPSINE* (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION
50 mcg. = .05 mg. = 1 ml.

Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

I. *Premedication*—Premedication (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered *intramuscularly* 30 to 60 minutes prior to surgery.

II. *Adjunct to General Anesthesia*—See Dosage Range Chart

III. *Adjunct to Regional Anesthesia*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

IV. *Postoperatively (recovery room)*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usual Children's Dosage: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 20 to 30 mcg. (0.02 to 0.03 mg.)(0.4 to 0.6 ml.) per 20 to 25 pounds is recommended.

DOSAGE RANGE CHART

TOTAL DOSAGE
Low dose—2 mcg./kg. (.002 mg./kg.)(.04 ml./kg.) SUBLIMAZE* injection. Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period. *Maintenance:* Additional dosages of SUBLIMAZE* injection are infrequently needed in these minor procedures.

Moderate dose—2-20 mcg./kg. (.002-.02 mg./kg.)(.04-0.4 ml./kg.) SUBLIMAZE* injection. Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential. *Maintenance:* 25 to 100 mcg. (0.025 to 0.1 mg.)(0.5 to 2.0 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

High dose—20-50 mcg./kg. (.02-.05 mg./kg.)(0.4-1 ml./kg.) SUBLIMAZE* injection. During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20-50 mcg. (.02-.05 mg.)(0.4-1 ml.) of SUBLIMAZE* injection with nitrous oxide oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH, and prolactin.

When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression.

The main objective of this technique would be to produce "stress free" anesthesia. *Maintenance:* Maintenance dosage (ranging from 25 mcg. (.025 mg.)(0.5 ml.) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

As a General Anesthetic
When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg./kg. (.05 to 0.1 mg./kg.)(1 to 2 ml./kg.) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg./kg. (.15 mg./kg.)(3 ml./kg.) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

OVERDOSAGE
Manifestations: The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; and oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

HOW SUPPLIED
2 ml. and 5 ml. ampoules—packages of 10.
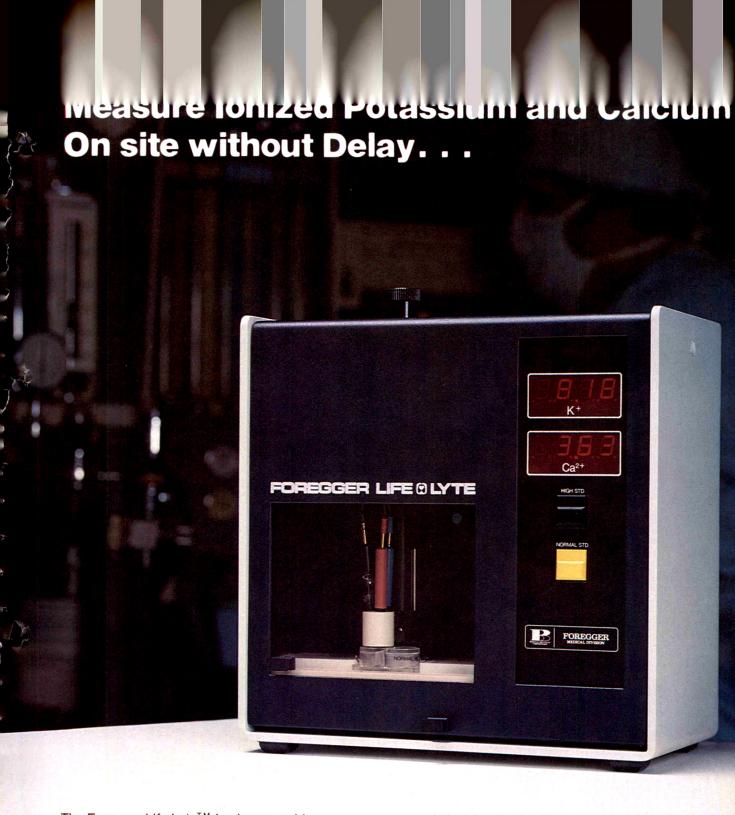**NDC** 50458-030-02 **NDC** 50458-030-05

10 ml. and 20 ml. ampoules—packages of 5.
NDC 50458-030-10 **NDC** 50458-030-20
(For intravenous use by hospital personnel specifically trained in the use of narcotic analgesics).
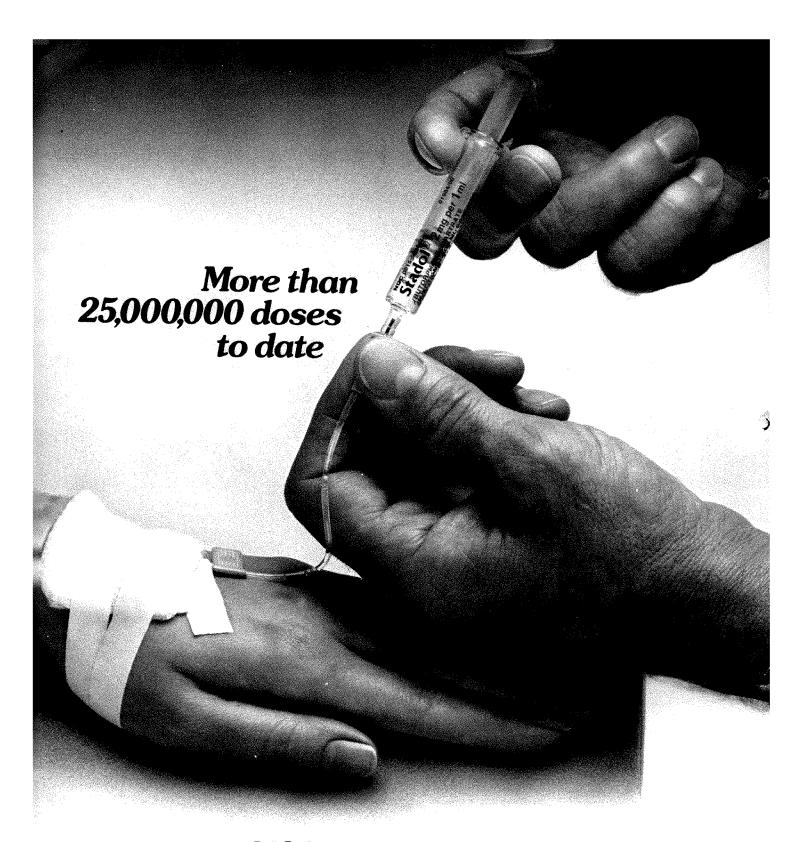
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JPI-255

Ethrane® (enflurane)

DESCRIPTION

ETHRANE (enflurane) (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether) (CHF2OCF2CHFCl) is a nonflammable inhalation anesthetic agent The boiling point is 56.5°C at 760 mm Hg and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C Vapor pressures can be calculated using the equation

$$\log_{10}P = A + B/T \quad \begin{aligned} A &= 7.967 \\ B &= -1678.4 \\ T &= °C + 273.16 \text{ (Kelvin)} \end{aligned}$$

The specific gravity (25°/25°C) is 1.517 The refractive index at 20°C is 1.3026-1.3030 The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C

Enflurane is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography) No stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary even in the presence of ultraviolet light Enflurane is stable to strong base and does not decompose in contact with soda lime and does not react with aluminum, tin, brass, iron or copper The partition coefficients of enflurane at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride

CLINICAL PHARMACOLOGY

ETHRANE (enflurane) is an inhalation anesthetic The MAC (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70 percent nitrous oxide—30 percent oxygen, and 1.17 in 30 percent nitrous oxide—70 percent oxygen

Induction and recovery from anesthesia with enflurane are rapid Enflurane has a mild, sweet odor Enflurane may provide a mild stimulus to salivation or tracheobronchial secretions Pharyngeal and laryngeal reflexes are readily obtunded The level of anesthesia can be changed rapidly by changing the inspired enflurane concentration Enflurane reduces ventilation as depth of anesthesia increases High PaCO2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported Enflurane provokes a sigh response reminiscent of that seen with diethyl ether

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation Progressive increases in depth of anesthesia produce corresponding increases in hypotension Heart rate remains relatively constant without significant bradycardia Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during enflurane anesthesia Enflurane anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias On the basis of studies in patients anesthetized with enflurane and injected with epinephrine containing solutions to achieve hemostasis in a highly vascular area (transsphenoidal surgery), it is recommended that 2 micrograms per kilogram (2 μg/kg) of epinephrine may be injected subcutaneously over a 10 minute period This may be repeated up to 3 times per hour

Example: Up to 10 ml of 1:100,000 epinephrine containing solution (10 μg/ml) may be injected subcutaneously over a 10 minute period in a 50 kilogram patient judged to have ordinary tolerance to epinephrine administration No more than 30 ml of 1:100,000 epinephrine containing solution (10 μg/ml) should be administered to such a patient per hour The concomitant administration of lidocaine enhances the safety of the use of epinephrine during enflurane anesthesia This effect of lidocaine is dose related All customary precautions in the use of vasoconstrictor substances should be observed

Example Two: Alternatively, up to 20 ml of 1:200,000 epinephrine containing solution (5 μg/ml) may be substituted for 10 ml of 1:100,000 solution in the above example

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with enflurane The NON-DEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height Neostigmine does not reverse the direct effect of enflurane

Biotransformation of enflurane in man results in low peak levels of serum fluoride averaging 15 μM/L These levels are well below the 50 μM/L threshold level which can produce minimal renal damage in normal subjects However, patients chronically ingesting isoniazid or other hydrazine containing compounds may metabolize greater amounts of enflurane Although no significant renal dysfunction has been found thus far in such patients, peak serum fluoride levels can exceed 50 μM/L, particularly when anesthesia goes beyond 2 MAC hours Depression of lymphocyte transformation does not follow prolonged enflurane anesthesia in man in the absence of surgery Thus enflurane does not depress this aspect of the immune response

Enflurane 0.25 to 1.0 percent (average 0.5 percent) provides analgesia equal to that produced by 30 to 60 percent (average 40 percent) nitrous oxide for vaginal delivery With either agent, patients remain awake, cooperative, and oriented Maternal blood losses are comparable These clinical approaches produce normal Apgar scores Serial neurobehavioral testing of the newborn during the first 24 hours of life reveals that neither enflurane nor nitrous oxide analgesia is associated with obvious neurobehavioral alterations Neither enflurane nor nitrous oxide when used for obstetrical analgesia alters serum BUN, creatinine, uric acid or osmolality The only difference in the use of these two agents for obstetrical analgesia appears to be higher inspired oxygen concentration that may be used with enflurane

Analgesic doses of enflurane, up to approximately 1 percent, do not significantly depress the rate or force of uterine contraction during labor and delivery A slowing of the rate of uterine contraction and a diminution of the force of uterine contraction is noted between the administration of 1 and 2 percent delivered enflurane, concentrations somewhere between 2 and 3 percent delivered enflurane may abolish uterine contractions Enflurane displaces the myometrial response curve to oxytocin so that at lower concentrations of enflurane oxytocin will restore uterine contractions, however, as the dose of enflurane progresses (somewhere between 1.5 and 3 percent delivered enflurane) the response to oxytocin is diminished and then abolished Uterine bleeding may be increased when enflurane is used in higher concentrations for vaginal delivery or to facilitate delivery by Cesarean section, however, this has not been demonstrated within the recommended dosage range (see DOSAGE AND ADMINISTRATION section) Mean estimated blood loss in patients anesthetized for therapeutic abortion with 1 percent enflurane in 70 percent nitrous oxide with oxygen is approximately twice that noted following therapeutic abortion performed with the use of a local anesthetic technique (40 ml versus 20 ml)

INDICATIONS AND USAGE

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia Enflurane may be used to provide analgesia for vaginal delivery Low concentrations of enflurane (see DOSAGE AND ADMINISTRATION) may also be used to supplement other general anesthetic agents during delivery by Cesarean section Higher concentrations of enflurane may produce uterine relaxation and an increase in uterine bleeding

CONTRAINDICATIONS

Seizure disorders (see WARNINGS)
Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics
Known or suspected genetic susceptibility to malignant hyperthermia

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity The latter may or may not be associated with motor movement Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups, it is self-limiting and can be terminated by lowering the anesthetic concentration This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension A reduction in ventilation and anesthetic concentrations usually suffices to eliminate seizure activity Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia Mental function testing does not reveal any impairment of performance following prolonged enflurane anesthesia associated with or not associated with seizure activity

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used Hypotension and respiratory exchange can serve as a guide to depth of anesthesia Deep levels of anesthesia may produce marked hypotension and respiratory depression

PRECAUTIONS

The action of nondepolarizing relaxants is augmented by ETHRANE (enflurane) Less than the usual amounts of these drugs should be used If the usual amounts of nondepolarizing relaxants are given, the time for recovery from neuromuscular blockade will be longer in the presence of enflurane than when halothane or nitrous oxide with a balanced technique are used

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation There is some elevation of glucose and white blood count intraoperatively Glucose elevation should be considered in diabetic patients Enflurane should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug

In susceptible individuals, enflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc The syndrome of malignant hyperthermia secondary to enflurane appears to be rare, by March 1980, 35 cases had been reported in North America for an approximate incidence of 1/725,000 enflurane anesthetics) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO2 absorption system (hot canister) PaO2 and pH may decrease, and hyperkalemia and a base deficit may appear Treatment includes discontinuance of triggering agents (e.g., enflurane), administration of intravenous dantrolene, and application of supportive therapy Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements Renal failure may appear later, and urine flow should be sustained if possible

Swiss ICR mice were given enflurane to determine whether such exposure might induce neoplasia Enflurane was given at ½, ⅛ and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life The mice were killed at 15 months of age The incidence of tumors in these mice was the same as in untreated control mice who were given the same background gases, but not the anesthetic

Exposure of mice to 20 hours of 1.2 percent enflurane causes a small (about ½ of 1%) but statistically significant increase in sperm abnormalities in contrast to these results, in vitro approaches to the study of mutagenesis (Ames test, sister chromatid exchange test, and the 8-azaguanidine system) have not shown a mutagenic effect of enflurane

Pregnancy Category B:
Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to enflurane There are, however, no adequate and well controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

ADVERSE REACTIONS

1. Malignant hyperthermia
2. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia
3. Hypotension and respiratory depression have been reported
4. Arrhythmias, shivering, nausea, and vomiting have been reported
5. Elevation of the white blood count has been observed

OVERDOSAGE

In the event of overdosage, the following action should be taken
Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered from a vaporizer during anesthesia should be known This may be accomplished by using
a) vaporizers calibrated specifically for enflurane.
b) vaporizers from which delivered flows can easily and readily be calculated

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by enflurane and that enflurane does not alter heart rate The use of anticholinergic drugs is a matter of choice

Surgical Anesthesia: Induction may be achieved using enflurane alone with oxygen or in combination with oxygen-nitrous oxide mixtures Under these conditions some excitement may be encountered If excitement is to be avoided a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the enflurane mixture In general, inspired concentrations of 2.0-4.5 percent enflurane produce surgical anesthesia in 7-10 minutes

Surgical levels of anesthesia may be maintained with 0.5-3 percent enflurane Maintenance concentrations should not exceed 3 percent If added relaxation is required, supplemental doses of muscle relaxants may be used Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred Hyperventilation should be avoided in order to minimize possible CNS excitation

The level of blood pressure during maintenance is an inverse function of enflurane concentration in the absence of other complicating situations Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia

Analgesia: Enflurane 0.25 to 1.0 percent provides analgesia for vaginal delivery equal to that produced by 30 to 60 percent nitrous oxide These concentrations normally do not produce amnesia See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section

Cesarean Section: Enflurane should ordinarily be administered in the concentration range of 0.5 to 1.0 percent to supplement other general anesthetics See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section

HOW SUPPLIED

ETHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles

Ethrane (enflurane) **10** years of experience confidence safety

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The Role of Conducting Airways in Gas Exchange during High-Frequency Ventilation—A Clinical and Theoretical Analysis

Ivan Eriksson, MD*

ERIKSSON, I.: The role of conducting airways in gas exchange during high-frequency ventilation—a clinical and theoretical analysis. Anesth Analg 1982;61:483-9.

Observed values for lung clearance index and mixing ratio appeared to be better than the calculated ideal values in seven of nine patients during high-frequency positive-pressure ventilation (HFPPV). The presence of substantial amounts of N_2 (9.2% to 22.5%) in the initial expired gas suggests that these findings are explained by amplified mixing of tidal gas with residual gas in the conducting airways secondary to the high gas flow velocity during inspiration. There was a moderate positive correlation ($r = 0.59$) between the amount of residual gas (N_2) present in the initial part of the expirate and the efficiency of nitrogen washout. A "functional" dead space for N_2 can be calculated. During HFPPV this was 125 ± 71 ml and during spontaneous breathing 354 ± 121 ml ($p < 0.001$), giving a V_D/V_T for N_2 of 0.38 ± 0.06 as compared with 0.84 ± 0.21 ($p < 0.001$) during spontaneous breathing. It also implies a more efficient washout of N_2 than of CO_2 (V_D/V_T approximately 0.75) during HFPPV.

Key Words: VENTILATION: high-frequency.

ONE OF THE MOST obvious changes in mechanical ventilatory techniques during recent years has been the increasing interest in high-frequency mechanical ventilation (1-3). The major advantages ascribed to this form of mechanical ventilation are low peak and mean airway pressures and less cardiovascular depression as compared with low ventilatory frequencies plus reflex suppression of spontaneous breathing (2-5).

The type of high-frequency ventilation developed by our group, high-frequency positive-pressure ventilation (HFPPV), is characterized by a ventilatory frequency of 60 breaths per minute and a relative insufflation time of 22% of the period time (2, 3). So far, HFPPV has been used clinically mainly for bronchoscopy and laryngoscopy under general anesthesia (6-9). Promising results with even higher ventilatory frequencies have recently been reported (10-12).

In healthy dogs, HFPPV in a volume-controlled mode with a low compressive ventilatory system and with a positive end-expiratory pressure (PEEP) of 5 cm H_2O has been shown to give a more efficient nitrogen washout during oxygen breathing than conventional intermittent positive-pressure ventilation (13). In patients undergoing diagnostic bronchoscopy because of suspected or verified pulmonary disease, indices of intrapulmonary gas distribution showed improvement during HFPPV as compared with spontaneous breathing (7).

The purpose of this paper is, on the basis of clinical results (7), to discuss and analyze mechanisms that may explain the efficiency of intrapulmonary gas distribution in terms of N_2 washout during mechanical ventilation at high ventilatory frequencies. Special attention will be paid to the role of the conducting airways.

Methods and Procedures

The experimental results presented and analyzed in this paper were obtained in nine subjects ranging in age from 50 to 63 years and undergoing diagnostic bronchoscopy. The research procedure of the investigation was approved by the Ethics Committee of The Regional Hospital in Örebro. All patients gave their informed consent to the investigation. The methods and procedures used here, together with patient data, have been described in detail previously (7).

The patients were mainly heavy smokers with symptoms and signs of pulmonary disease. They were examined by means of a non-rebreathing multiple breath nitrogen washout technique with oxygen for determination of intrapulmonary gas distribution and functional residual capacity (FRC), first during spontaneous breathing, then during HFPPV under general anesthesia and muscular relaxation. Expired gas volumes for calculation of FRC and tidal volume (V_T) were measured in a Tissot tank spirometer. After corrections for apparatus dead space, gas impurities, and nitrogen dissolved in body fluids, FRC was calculated. The anatomic dead space was measured by the equal area of Fowler (14) in two patients. Gas volumes were corrected to BTPS. The gas for analysis of the N_2 concentration was taken at a level just above the lips during spontaneous breathing and from the endotracheal tube at the level of the lips during HFPPV. Gas fractions were measured by a mass spectrometer (Centronic MGA-200, 20th Century Electronics Ltd, UK) and recorded on paper (Devices MX412, Devices Ltd, UK). The 90% response time for this system to an abrupt change from air to oxygen was 0.12 seconds. The effect of gas sampling (20 ml/min) on the measurements was considered negligible. The signal from the mass spectrometer was also recorded on an FM tape recorder with a frequency range of 17,500 Hz (Tandberg TIR 115, Tandberg A/S, Norway). For the subsequent calculation, the signal from the tape recorder was fed into a sample and hold

amplifier with a sampling frequency of 2400 samples/sec, e.g., each breath during HFPPV was divided into 2400 sections. A peak detector selected the highest value of each breath and fed it into a desk computer (PET 2001-8, Commodore Business Machines, CA) via an A/D converter. The end-expired N_2 concentration of each breath was thus obtained and corrected for gas impurities and nitrogen dissolved in body fluids.

Calculations

Ventilatory efficiency as a whole may be expressed as a lung clearance index (LCI) (15). It may be written as

$$LCI = \frac{n \cdot V_T}{FRC} \qquad (1)$$

where n is the number of breaths required to reduce end-expired N_2 concentration (FE) to 2% (n-observed).

The basic equation for washout of an inert gas from a uniformly ventilated space (16) is

$$FA_n = FA_0 \cdot w^n \qquad (2)$$

where FA_n is the alveolar concentration of N_2 after n breaths and FA_0 is the alveolar concentration before washout. FE is considered to correspond to FA.

The alveolar dilution factor w is defined as

$$w = \frac{FRC}{FRC + (V_T - V_D)} \qquad (3)$$

where V_D is the volume of the anatomic dead space.

Equation 2 may be solved for the expected (or ideal) n required to reduce FE from 80% to 2% (n-expected).

$$n = \frac{\log 0.025}{\log w} \qquad (4)$$

If this value for n, based on the actual magnitudes of V_T, V_D, and FRC, is substituted in equation 1, the ideal or expected value for LCI (LCI-expected) is obtained (17). As LCI-expected takes into consideration changes in FRC, V_T, and V_D, it should be suitable for comparisons at different ventilatory frequencies.

A mixing ratio (MR) (17) may be calculated as the ratio of the n-observed to the n-expected required to reduce FE to 2%. This index differs from the pulmonary clearance delay of Fowler et al (16) in that curve fitting is not required and that only the volume required to reduce FE to 2% is considered. Further, the lung is simplified into a single alveolar and a single dead space compartment.

V_D is usually considered to decrease after endotra-

ABBREVIATIONS	
SB	spontaneous breathing
HFPPV	high-frequency positive-pressure ventilation
PEEP	positive end-expiratory pressure
V_T	tidal volume (ml)
V_D	anatomic dead space (ml)
FRC	functional residual capacity (ml)
n-observed	observed number of breaths required to reduce end-expired N_2 concentration to 2%
n-expected	expected or ideal number of breaths required to reduce end-expired N_2 concentration from 80% to 2%
MR	mixing ratio
LCI-observed	observed lung clearance index
LCI-expected	expected or ideal lung clearance index
"Functional" V_D	functional or effective dead space for N_2
FA_0	alveolar concentration of N_2 before washout
FA_n	alveolar concentration of N_2 after n breaths
FE	end-expired N_2 concentration
w	alveolar dilution factor

cheal intubation, secondary to bypass of the upper airways by the endotracheal tube. However, as the volume of the conducting airways is also related to their distention, it has been assumed here that the PEEP of approximately 3 to 4 cm H_2O present during HFPPV, together with the muscular relaxation, compensates for this reduction (18, 19). This is supported by actual measurements of V_D according to Fowler (14) in two of our patients (S.E. and R.E.), in whom no difference in V_D was found between spontaneous breathing and general anesthesia with intubation. V_D has therefore been considered to be the same during spontaneous breathing and intubation as found by Hedenstierna and McCarthy (19) and has been calculated from body size as described by Hart et al (20). Further, with proportional changes in volume, V_D has a lesser effect than V_T on expected values.

Statistics

All differences reported were tested for statistical significance by means of Student's t-test for paired data. A probability level of less than 0.05 was considered statistically significant. Linear regression lines were made by the method of least squares and the coefficients of correlation are the product moment correlation of Pearson. To test the null hypothesis of a zero correlation, a one-tailed t-test, n-2 df was used, the alternative hypothesis stating a positive correlation (Fig 4).

Results

During spontaneous breathing n-observed was always greater than n-expected (Table). During HFPPV n-observed was less than n-expected in seven of nine patients. This gave a MR greater than 1 in all patients during spontaneous breathing and a MR less than 1 in seven of nine patients during HFPPV (Fig 1; $p <$ 0.001). LCI-observed and LCI-expected behaved analogously (Table).

The upper two curves in Fig 2 show N_2 washout from one patient (B.P.) with an efficient washout (see Table) during spontaneous breathing and during HFPPV. During spontaneous breathing both the ventilatory volume and the number of breaths required were greater than during HFPPV (figures corrected for gas impurities and N_2 dissolved in body fluids are shown in Table). During HFPPV in patient B.P. there was a rapid decrease of FE, which reached 2% after 18 seconds. For comparison, the curve from another patient (P.-I.S.) with one of the slowest washouts is shown during HFPPV with a FE of 2% being reached

TABLE
Patient Data during Spontaneous Breathing/High-Frequency Positive-Pressure Ventilation*

	S.F.	B.E.	A.O.	L.W.	H.K.	S.E.	B.P.	P.-I.S.	R.E.	Mean ± SD	Statistical significance
Ventilatory frequency (breaths)	20/60	10/60	12/60	16/60	15/60	13/60	17/60	13/60	15/60	15 ± 3.0/60 ± 0	NS
V_T (ml)	281/358	648/311	636/368	300/247	406/316	405/300	312/376	439/310	400/393	423 ± 137/331 ± 46	NS
V_D (ml)	147	160	173	124	160	145	138	177	184	156 ± 20	NS
FRC (ml)	1738/1552	1352/1614	1942/2154	1850/1963	1329/1741	2237/2498	1339/1683	2111/1657	1532/1494	1714 ± 346/1820 ± 330	p < 0.001
n-observed	179/24	73/50	57/28	119/46	92/41	120/49	53/18	122/45	107/39	102 ± 39/38 ± 12	NS
n-expected	58/29	12/41	17/43	41/61	22/43	34/61	30/28	32/48	28/28	30 ± 14/42 ± 13	p < 0.001
MR	3.08/0.83	6.11/1.21	3.31/0.61	2.90/0.75	4.22/0.95	3.57/0.80	1.75/0.65	3.87/0.91	3.82/1.40	3.63 ± 1.10/0.90 ± 0.26	p < 0.001
LCI-observed	26.9/5.5	33.9/9.6	18.8/4.4	30.1/5.3	28.0/7.4	21.7/5.9	12.3/4.0	25.4/8.4	27.9/10.1	25.0 ± 6.5/6.7 ± 2.2	p < 0.001
LCI-expected	8.7/6.7	5.7/8.0	5.7/7.3	6.6/7.6	6.6/7.8	6.0/7.4	7.0/6.2	6.6/8.9	7.3/7.4	6.7 ± 0.9/7.5 ± 0.8	NS
"Functional" V_D	225/98	575/187	507/36	263/112	350/151	335/106	215/23	374/168	346/243	354 ± 121/126 ± 71	p < 0.001
Initial expired N_2-concentration (%)	/17.4	/18.0	/18.6	/26.4	/13.6	/22.5	/16.7	/12.6	/9.2	/17.2 ± 5.2	

* V_D/V_T ratio for N_2 during spontaneous breathing is 0.84 ± 0.21 and during HFPPV 0.38 ± 0.06 ($p < 0.001$).
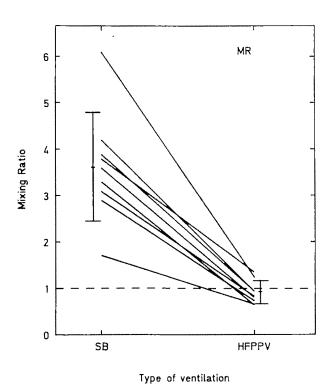
Fig 1. Mixing ratio (MR) during spontaneous breathing (SB) before surgery and during high-frequency positive-pressure ventilation (HFPPV). Bars indicate means ± SD; $p < 0.001$.
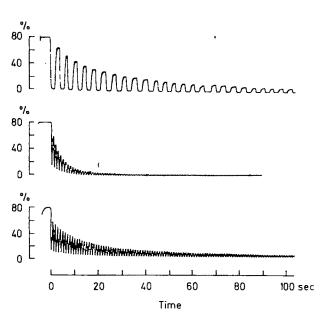
Fig 2. N_2 washout curves during spontaneous breathing and during HFPPV for patient with fast nitrogen washout (B.P., upper two curves). For comparison N_2 washout curve for patient with slow washout (P.-I.S., lower curve) is given during HFPPV. Actual recordings not corrected for gas impurities or N_2 dissolved in body fluids.

after 45 seconds. The N_2 fraction in initial expired gas taken from the upper part of the endotracheal tube after the first breath of O_2 was higher (16.7%) in the patient with the more rapid washout of N_2 than in the patient with a slow washout (12.6%).

A detailed analysis of N_2 concentration curves obtained in patient B.P. (Fig 2, upper two curves), beginning with the first expiration of a N_2 washout recording during spontaneous breathing (Fig 3), shows the classic pattern with a fairly clear separation between gas from the conducting airways and gas from the alveolar space, and an alveolar plateau (14). The initial expirate consists of inspired O_2 (with impurities). During HFPPV the N_2 concentration curves were different from those during spontaneous breathing in all patients. The major differences were: (a) The initial horizontal part of the N_2 concentration curve during expiration, which represents gas expired from the endotracheal tube and from the conducting airways, obviously did not represent the last of the inspired tidal volume of oxygen, as it contained a substantial amount of N_2 (FE = 16.7%; Fig 2). (b) The expired N_2 concentration started to increase early and increased
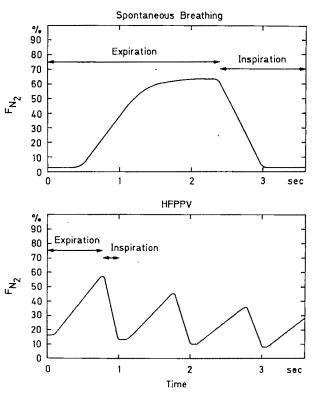
Fig 3. Details of changes in N_2 concentration in gas obtained from upper end of conducting airways immediately after start of O_2 breathing during spontaneous breathing and during HFPPV in one patient (B.P.).
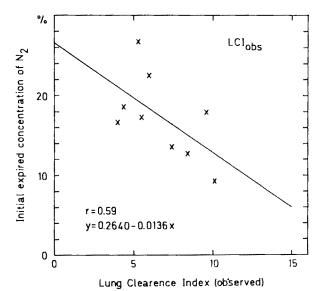
Fig 4. Initial expired N_2 concentration plotted against observed lung clearance index (LCI-observed) (r = 0.59; p < 0.05).

almost linearly without any transition zone between gas from the conducting airways and gas from the alveolar space and thus there was no alveolar plateau as was seen during spontaneous breathing.

When plotted against each other (Fig 4), the initial expired N_2 concentrations are inversely related to LCI-observed (r = 0.59; p < 0.05), i.e., a high initial expired N_2 concentration corresponds to an efficient washout of N_2.

Discussion

In 1975 Scherer et al (21) reported that the effective axial diffusivity increased with increasing gas flow rate. However, their results were obtained with laminar gas flows and an axial gas velocity of 2 to 100 cm/sec. The axial velocity during HFPPV in the present study was in the order of 2500 to 3000 cm/sec, i.e., much higher and corresponding to peak Reynold's numbers of well above 10,000 and turbulent flow. In the human lung Reynold's numbers progressively decrease as a result of the increasing total cross-sectional area of the distal airways, and the most turbulent flow will be in the trachea or the endotracheal tube and in the large airways. The flow conditions prevailing during HFPPV therefore suggest increased gas mixing secondary to turbulence in the conducting airways. Recently Fredberg (22) also showed that high flow velocities may support gas exchange by "augmented diffusion" in the airways. It was not possible, in this study, to differentiate between the effects of the gas mixing processes discussed above and the eventual presence of differences

in axial velocity or a coaxial gas flow. The reasoning is in line with the observed presence of substantial amounts of N_2 (residual gas) 5 to 8 cm from the outer opening of the endotracheal tube at the end of inspiration, as well as the increase in N_2 concentration early during expiration (Figs 2 and 3) while the conducting airways are still being emptied. It implies that the end-inspired gas is also, to some degree, being used for N_2 washout, i.e., a greater fraction of the tidal volume is being effective in N_2 washout during HFPPV than during spontaneous breathing.

The amount of N_2 eliminated is represented by the area under the N_2 concentration curve. Thus, if gas mixing in the large airways was the only source of variance in nitrogen washout, the most efficient washout should take place where the initial expired N_2 concentration is highest. However, the correlation between initial expired N_2 concentration and LCI-observed (Fig 4) is not particularly strong. This is perhaps not surprising, as other factors, e.g., differences in the conditions of the distal airways between the patients are also of importance.

The findings of values for LCI-observed that were less than calculated ideal, and also of values of MR less than 1 (Table, Fig 1) during HFPPV imply a functionally decreased dead space for N_2. Such a "functional" dead space for N_2 operating during HFPPV may be calculated. By inserting the expression of w from equation 3 into equation 4, we obtain

$$n = \frac{\log 0.025}{\log \dfrac{FRC}{FRC + (V_T - V_D)}} \quad (5)$$

If the observed values for n, FRC, and V_T are used, then V_D in equation 5 is the functional V_D for N_2, consistent with LCI-observed and MR. Equation 5 may be solved by using logarithms and rearranging:

$$V_{D_{functional}} = FRC + V_T - \frac{FRC}{10^{\log 0.025/n}} \quad (6)$$

The calculated values for the functional dead spaces are shown in the Table. For a patient with one of the most efficient N_2 washouts during HFPPV (Å.Ö.) functional dead space is thus 36 ml and for the patient with the slowest washout (R.E.) it is 243 ml. A LCI-observed or MR less than the expected then implies that the interface between the alveolar space and the conducting airways has moved outward, contrary to observations at lower gas flow velocities (21, 23).

With increasing inspiratory gas flow velocities, the differences between dependent and nondependent regions of the lung have been shown to decrease,

giving a more even topographic distribution of inspired gas (24-26). This is also in line with the efficient N_2 washout during HFPPV and a decrease in the functional V_D for N_2. However, as both ventilation and perfusion normally go more to dependent lung regions, this alteration toward a more even topographic distribution of inspired gas should give an increased V/Q mismatch with increased alveolar dead space for CO_2 (18) and increased venous admixture. A decrease in pulmonary arterial pressure associated with general anesthesia would further increase V/Q mismatch. This implies a considerable alveolar dead space for CO_2 and provides an explanation for the difference between the high ventilatory volumes (approximately 19 L/min in this study) that were necessary for ventilatory steady states with adequate elimination of CO_2, on the one hand; and the very efficient N_2 washout on the other, as N_2 is not dependent of alveolar perfusion for washout. The V_D/V_T has been shown to be approximately 0.75 for CO_2 during HFPPV (27) but is approximately 0.38 for N_2 in this study (from Table). The physiologic dead space for CO_2 is thus much larger than the volume of the conducting airways, contrary to the small functional dead space for N_2. Therefore, an efficient washout of N_2 is not proof of an efficient alveolar gas exchange.

In conclusion, it seems that during HFPPV, the high gas flow velocity during inspiration gives an increased gas mixing in the conducting airways. This is probably secondary to turbulence and "augmented diffusion." It causes residual gas to be present in the conducting airways at end-inspiration and is compatible with a displacement of the transition zone between tidal and residual gas toward the outer opening of the conducting airways. The functional V_D for N_2 can thus be smaller than the volume of the conducting airways as there is no alveolar dead space for N_2. The efficiency of N_2 washout during HFPPV seems to be related to the amount of residual gas present in the conducting airways at the end of inspiration. A more even topographic distribution of inspired gas during HFPPV may decrease elimination of CO_2, whereas washout of N_2 is efficient.

ACKNOWLEDGMENT

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Nonrespiratory Side Effects of Epidural Morphine

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BROMAGE, P. R., CAMPORESI, E. M., DURANT, P.A.C., AND NIELSEN, C. H.: Nonrespiratory side effects of epidural morphine. Anesth Analg 1982;61:490-5.

Ten healthy young male volunteers received in random sequence 10 mg of morphine sulfate intravenously and by lumbar epidural route during two 26-hour study sessions, in order to observe the appearance and resolution of the following side effects: (a) pruritus, (b) nausea, (c) vomiting, (d) urinary dysfunction. With the exception of one subject, who experienced transient (2 hours) nausea, none of the subjects experienced any adverse side effects after the intravenous morphine. However, all subjects experienced some degree of one or more complications, starting 3 hours after the epidural administration: generalized pruritus started at 3.0 ± 0.3 hours (nine of 10 subjects, mean ± SD) and lasted 5.3 ± 4.0 hours. Nausea occurred in six subjects at 4.0 ± 0.6 hours, and lasted for 3.0 ± 2.1 hours; vomiting occurred at 6.3 ± 2.0 hours in five of the nauseated subjects. Urinary retention of varying intensity and duration appeared in nine subjects and required pharmacologic intervention in six subjects. Serum levels of unmodified morphine were measured at various times after administration during both sessions and did not correlate with the incidence or temporal appearance of side effects. Serial evaluation of dermatomal level of hypalgesia to ice and pin scratch demonstrated a progressive spread in the rostral direction after epidural morphine; trigeminal areas were affected by 9 hours in five of the 10 subjects. The stereotyped sequence of side effects after 10 mg of morphine by the epidural route can be interpreted to reflect widespread dispersion of morphine throughout the subarachnoid and ventricular cerebrospinal fluid.

Key Words: ANALGESICS: morphine; ANESTHETIC TECHNIQUES: epidural, morphine.

INTRASPINAL narcotics by the subarachnoid or epidural route produce segmental analgesia of great power and duration (1, 2). The intensity of analgesia matches that conferred by intraspinal local anesthetics (3), but without the disadvantage of sympathetic efferent blockade (4). Unfortunately the nonrespiratory side effects of pruritus, nausea, and urinary retention associated with intraspinal narcotic administration are common enough to question the widespread clinical use of this approach. Moreover, reports of delayed, profound, and prolonged respiratory depression make close and continuous surveillance an essential condition for many hours after

epidural morphine has been administered (5-8). These different side effects have been ascribed to various causes including morphine preservatives (9, 10), histamine release (8), and opiate receptor occupation within the brainstem (11).

Both the quality of epidural narcotic analgesia and severity of side effects seem to be dose dependent (12). Our earlier study of epidural narcotics in volunteers used the lipophilic drugs hydromorphone and methadone in doses equivalent to 5 to 7.5 mg of morphine, and we obtained a strictly limited segmental analgesia with very few side effects (4). Limited segmental spread has also been reported by other authors (13) when small doses of epidural morphine (4 to 5 mg) were used and when observations did not extend beyond 3 hours after epidural administration. However, our subsequent clinical experience after upper abdominal surgery showed that somewhat larger doses, equivalent to 8 to 10 mg of morphine, were required to achieve effective postoperative analgesia as judged by spirometric criteria (3). Therefore in this investigation we selected a dose of epidural morphine (10 mg) that would be adequate to relieve acute severe pain under most clinical circumstances,

and the time of study was extended for a period greater than 24 hours in order to observe the evolution and regression of delayed side effects. The adverse effects that were encountered showed a high degree of predictability in their temporal appearance, and the stereotyped pattern of emergence of these complications suggest that a common etiologic mechanism may underlie all of them. Major respiratory side effects also occurred during the course of this study; these respiratory observations will be published separately.

Methods

The nonrespiratory side effects of preservative-free morphine were studied in 10 men aged 18 to 33 years. All were healthy and three were trained athletes. Body weight ranged between 62 and 110 kg (mean 82.6 ± 18 (SD) kg). The subjects were fully informed and each was given a comprehensive pretest physical examination, including electrocardiogram (ECG), urinalysis, and blood chemistry. The protocol received institutional approval.

Each subject underwent two 26-hour periods of study, 2 to 4 weeks apart. Morphine, 10 mg, was administered intravenously at one session, and by the lumbar epidural route at the other session in randomized sequence. All subjects fasted from midnight and had consumed no caffeine-containing foods or beverages from 10:00 p.m. the preceding evening. The subjects were studied on a hospital stretcher bed in a quiet environment. Between periods of measurement they were permitted to move about as freely as they wished. The following measurements were made at each session with the subjects reclining in a 20° head-up position.

Serum Morphine Concentrations

Blood (10 ml) was drawn from a forearm vein for serum morphine assay at the following times: control (before injection of test drug) and then 0.5, 1, 3, 6, 10, 16, and 22 hours after injection. The contralateral arm was used for sampling after intravenous administration. Blood was drawn by a 20-gauge needle into glass syringes, and centrifuged in glass Vacutainers. The serum was transferred to Teflon tubes and frozen until assayed by high-pressure liquid chromatography (14).

Segmental Cutaneous Hyposensitivity

Sensitivity to ice, pin scratch, and pin prick was tested on the skin of thighs, abdomen, chest, neck, and face at the following times: before administration of morphine and at 10, 20, 30, and 45 minutes, and 1, 3, 6, 10, 16, and 22 hours, or more often.

Side Effects

The onset and duration of pruritus, nausea, and vomiting were noted. The subjects were requested to void shortly after morphine administration. Thereafter, all voided urine was collected and measured. Subjects were also asked to describe any changes of sensation or bodily functions that they experienced after receiving intravenous and epidural morphine.

Morphine Administration

Sterile, coded ampules containing 10 mg of morphine sulfate in preservative-free isotonic saline were supplied by A. H. Robins Company Research Laboratories. The mode of administration has been described elsewhere (14). In summary, 10 mg of morphine was injected intravenously over a period of 3 minutes at one session. At the other session an epidural catheter was inserted at the second lumbar interspace. Catheter placement was validated by a preliminary dose of 10 ml of 2% chloroprocaine. Thirty minutes after complete regression of the chloroprocaine block 10 mg of morphine sulfate in 10 ml of normal saline was injected through the catheter, and the catheter and filter were flushed with 1.0 to 1.5 ml of normal saline. Subjects maintained a supine posture for the next 10 to 15 minutes, and then the catheter was withdrawn.

Management of Complications

Side effects were not treated except when it was considered that their continuance might prove harmful to the subjects. Prolonged urinary retention was treated by pharmacologic means if two or more of the following indications existed: (a) failure to void at 18 hours, (b) bladder discomfort, (c) bladder palpable above the symphysis pubis. Subcutaneous bethanechol (Urecholine), 5 mg, was given initially. If this failed to initiate micturition, intravenous naloxone, 0.4 mg, was given slowly to reverse the effects of the morphine and the experiment was terminated.

Results

The pattern of spread of hypalgesia has been described elsewhere (14) and this effect will be referred to only insofar as it coincides with the temporal

appearance of the nonrespiratory complications observed in this study.

Intravenous Morphine

After intravenous morphine all subjects experienced a transient sleepiness and feeling of relaxation lasting approximately 1 hour, but all were alert and active by the 5th hour. Nine of the 10 subjects were able to ingest normal amounts of food and drink at meal times without discomfort. One subject had mild nausea lasting for 2 hours after intravenous morphine. No dysuria or retention of urine occurred. None of the subjects experienced itch and none vomited.

The average concentration of morphine in peripheral venous blood was 26.2 ± 7.4 ng/ml at the first sampling period ½ hour after intravenous injection. Blood concentrations decreased rapidly and reached insignificant levels by the 6th hour as shown in Fig 1.

Epidural Morphine

Blood concentrations of morphine at the first sampling period were higher than after intravenous injection, with an average value of 41.5 ± 9.7 ng/ml. Thereafter concentrations decreased and, as with the intravenous route, reached insignificant levels by the 6th hour.

No side effects were encountered during the first 2 hours after epidural administration, but by the 3rd hour all subjects showed signs of diminished intellectual activity and concentration. From the 3rd hour onward one or more of the complications of pruritus, nausea, vomiting, and retention of urine developed in all of the 10 volunteers.
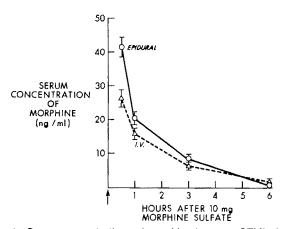
Fig 1. Serum concentrations of morphine (mean ± SEM) after intravenous and lumbar epidural administration of 10 mg of morphine sulfate in 10 subjects; △- - -△, intravenous; O———O, epidural.

Pruritus

Itching of the thighs and groin occurred in one of the 10 subjects 2 hours after morphine injection. Then with remarkable punctuality itching of the face, scalp, and neck, and sometimes trunk and legs commenced after 165 to 225 minutes in nine subjects and precisely at 180 minutes in six of the nine. Pruritus of varying intensity lasted for 5.3 ± 4.0 hours and then disappeared. In two subjects with severe pruritus and urinary retention naloxone, 0.4 mg IV relieved both the retention and the itching within a few minutes.

Nausea

Nausea occurred in six subjects. With one exception it always appeared after the onset of pruritus, with an average onset time of 4.0 ± 0.6 hours and lasting for 3.0 ± 2.1 hours.

Vomiting

Vomiting occurred later still at 6.3 ± 2 hours in five of the nauseated subjects. Vomiting was usually sudden with little forewarning and was confined to a single episode in three subjects, two episodes in one subject, and repeated bouts for six hours in the other volunteer.

Meiosis

By the 6th to 9th hour all subjects had suffused conjunctivae and pupils that were small and poorly reactive to light.

Cardiovascular Depression

Resting blood pressure showed a steady downward trend over the first 10 hours, but the differences were not statistically different from control resting levels.

Urinary Retention

None of the subjects experienced any difficulty of micturition after intravenous morphine and all had voiding volumes of less than 500 ml. By contrast, all 10 subjects experienced some degree of urinary difficulty after epidural morphine. Nine subjects were unable to void in the interval between ½ hour and 10 hours, but none complained of painful bladder distention during that time. The distribution of voiding time intervals is shown in the Table. One subject had minimal difficulty in urinating at 5½ hours. He complained of mild hesitancy lasting a few minutes followed by "a diminished sensation" while voiding 525

TABLE

**Comparison of Voiding Times in 10 Subjects after
Intravenous and Epidural Morphine (10 mg)**

Interval after morphine injection	No. of patients	
	Intravenous	Epidural
hr		
0–5	10	—
5–10	—	1
10–15	—	1
15–20	—	5
20–25	—	3

ml of urine. Three subjects voided spontaneously after several unsuccessful attempts 11 to 15 hours after epidural morphine, but the urinary volumes were large (500 ml, 720 ml, and 860 ml). The remaining six subjects had one or more indications for treatment after 15 hours. Bethanecol, 5 mg, subcutaneously was successful in only two of these subjects. Two subjects complained of increasing bladder discomfort after receiving bethanecol, but no subjective effect occurred in the remaining two. The four subjects who failed to respond to bethanechol were given naloxone, 0.4 mg IV, and all four were able to initiate voiding within 10 minutes. Three of these four subjects voided without appreciable interruption and passed volumes of 325 ml, 425 ml, and 850 ml, respectively. The fourth subject voided promptly after naloxone, but subsequent flow became intermittent and he required 20 minutes to empty his bladder of approximately 525 ml.

None of the volunteers encountered any subsequent urinary difficulty after 24 hours following epidural morphine administration.

Rostral Spread of Hypalgesia

The pattern of rostral spread of hypalgesia after epidural morphine has been described elsewhere (14). In Fig 2 is summarized the temporal sequence of onset, duration, and regression of nonrespiratory side effects in relation to the upper segmental level of hypalgesia to ice and pin prick. It can be seen that generalized pruritus began when the cephalad level of cutaneous hypalgesia reached the mid to upper thoracic segments. Nausea and vomiting occurred a little later when hypalgesia extended to the upper cervical territory.

Discussion

Serum concentrations of morphine were not directly related to the incidence or temporal appearance
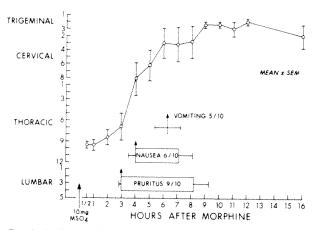
FIG 2. Incidence, time of onset, and duration of nonrespiratory side effects after 10 mg of lumbar epidural morphine (mean ± SEM) related to segmental spread of cutaneous hypalgesia to ice and pin scratch in 10 subjects.

of side effects in this series, and the role of morphine in the blood compartment may be dismissed as relatively insignificant, except insofar as local blood flow determines the length of time that injected agents remain in the epidural space.

Although no itching occurred after intravenous morphine, pruritus was the earliest, the most punctual, and the most consistent complication of epidural morphine. It involved the head and trunk in all of the nine subjects who were affected. Itching has been ascribed to histamine release (8) or to the presence of preservatives in the morphine (9, 10). However, in this series there were no stigmata of histamine release, and no preservatives were used. On the other hand, the epidural route of administration appeared to be all important, and generalized itching, including in the head and neck, began 3 hours after injection at a time when cutaneous hypalgesia was beginning to spread cephalad at its fastest rate. At the same time the hands began to become hypalgesic as measured by the cold pressor response test (14), indicating that appreciable quantities of morphine had ascended to the neck and penetrated the dorsal horn of the cervical spinal cord.

Later, as cutaneous hypalgesia rose to the cervical and trigeminal segments, nausea and vomiting developed, hypalgesia to cold pressure response test intensified in the hands, and the pupils became small and poorly reactive, indicating that all of these factors were probably linked to a common causal phenomenon.

Urinary retention proved to be the most troublesome complication. It developed insidiously and appeared to be related to partial loss of bladder sensa-

tion. Little or no discomfort accompanied bladder distention until urinary volumes had become large. Normal bladder capacity is taken to be approximately 500 ml (15) and so three of the 10 subjects probably experienced some degree of bladder overdistention. The parasympathomimetic action of bethanechol has been recommended as a first line of treatment for urinary retention after epidural morphine, but we found it to be virtually useless under these circumstances, and in two cases 5 mg of bethanechol did no more than increase bladder discomfort and distress. By contrast, naloxone was immediately successful in initiating normal micturition when bethanechol had failed. All of these complications may be explained as the direct or indirect results of cephalad spread of partial deafferentation.

Initial studies of morphine on the spinal cord had suggested that the action at the dorsal horn is purely antinociceptive (16, 17). However, subsequent clinical experience has shown that some other sensory modalities are also affected, including the cutaneous sensation of cold and pin scratch (4). It has been assumed that spinal narcotics have a localized segmental effect (1) and small doses of lipid-soluble drugs such as methadone and hydromorphone do indeed produce segmental hypalgesia which is quite precisely localized (4). However, poorly lipid-soluble agents such as morphine are retained in the spinal fluid for long periods, so they can float rostrally for great distances in the subarachnoid space before they diffuse into the lipid tissues of the cord (3). Radiologic evidence shows that water-soluble contrast media such as metrizamide travel from the lumbar thecal space to the basal cisternae within minutes and through the ventricular pathway to the fourth and lateral ventricles within 1 to 3 hours (18). The pattern of emergence of side effects that we have observed can be traced by inference along the same route with morphine acting on sensory relay nuclei near the surface of the upper spinal cord and brainstem. Some of these nuclei may be close to the subarachnoid pial surface, whereas others may lie close beneath the ependymal lining of the floor of the fourth ventricle.

The precise neurologic basis for itching is still uncertain, but pruritus is commonly seen in conditions where sensory modulation is disturbed, as in multiple sclerosis (19, 20), diabetic neuropathy (21), and occasionally during complete sensory blockade (22). Morphine has been shown to have a facilitatory action on non-nociceptive neurons in the dorsal horn (23). In animals paroxysms of scratching follow injection of morphine into the cisterna magna (24). A similar phenomenon is reported after the application of tetanus toxin to the caudal trigeminal nucleus (25). We postulate that the punctual appearance of generalized itching 3 hours after epidural morphine is due to a perturbation of sensory input arising from rostral spread of morphine within the spinal fluid to the level of the cervical extension of the trigeminal nucleus or subnucleus caudalis (26). Nausea and vomiting 1 to 3 hours later could be due to modulation of afferent input at the area postrema (27) or at the nucleus of the tractus solitarius, a key relay station in the visceral sensory network. The nucleus of the tractus solitarius may be affected directly by morphine diffusing through the ependymal floor of the fourth ventricle, or it might be affected indirectly by suppression of trigeminosolitary fibers after penetration to the trigeminal nucleus from the pial surface of the medulla and upper cervical cord (28).

In conclusion, the side effects of 10 mg of epidural morphine reflect widespread dispersion of morphine throughout the subarachnoid and ventricular cerebrospinal fluid. The subsequent modulation of afferent input has protean manifestations involving both cutaneous and visceral sensation, as well as visceral functions that are dependent upon a normal traffic of afferent input. It must be pointed out that the high incidence and severity of nonrespiratory side effects encountered in this series was related to the generous dose of epidural morphine chosen for the investigation. We suggest that smaller doses may be more appropriate in most clinical situations.

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Serum Oncotic Pressure and Oncotic-Hydrostatic Pressure Differences in Critically Ill Patients

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SISE, M. J., SHACKFORD, S. R., PETERS, R. M., AND VIRGILIO, R. W.: Serum oncotic pressure and oncotic-hydrostatic pressure differences in critically Ill patients. Anesth Analg 1982;61:496-8.

The possible influence of serum colloid oncotic pressure (COP) and the gradient between COP and pulmonary capillary wedge pressure (COP-PCWP) on respiratory insufficiency and survival was studied prospectively in 77 critically ill surgical patients by daily simultaneous measurements of COP, PCWP, and intrapulmonary shunt (Qs/Qt). Mean ages of survivors (N = 51) and nonsurvivors (n = 26) were 46 ± 3 years (survivors) and 58 ± 4 years (nonsurvivors), respectively ($p < 0.01$). Lowest value of COP was similar in survivors (15 ± 1 torr) and in nonsurvivors (14 ± 1 torr). Lowest value of COP-PCWP in survivors was 3 ± 1 torr and −1 ± 2 torr in nonsurvivors ($p < 0.05$). The difference in COP-PCWP was secondary to a significantly greater PCWP in nonsurvivors (16 ± 1 torr) than in survivors (12 ± 1 torr) ($p < 0.01$). For each patient, Qs/Qt measured at the time of lowest measured COP was not significantly different between survivors and nonsurvivors (0.18 ± 0.01 in survivors and 0.20 ± 0.01 in nonsurvivors) and measured at lowest COP-PCWP (0.18 ± 0.01 in survivors, and 0.21 ± 0.01 in nonsurvivors). No correlation was found between either lowest COP or lowest COP-PCWP and Qs/Qt. Progressive respiratory insufficiency was not a dominant factor in determining respiratory insufficiency was not a dominant factor in determining mortality. These data suggest that COP alone is not a critical factor in determining either survival or respiratory insufficiency as measured by Qs/Qt in critically ill surgical patients.

Key Words: VENTILATION: oncotic pressure; BLOOD: oncotic pressure; LUNGS: pulmonary capillary pressure, shunt.

THE RELATIONSHIP between serum colloid osmotic pressure (COP) and capillary hydrostatic pressure is a determinant of fluid movement across capillary membranes was proposed by Starling in 1896 in what has become known as the Starling hypothesis (1). The Starling equation defines the balance of forces that control fluid effusion (2):

$$J_V = K_F \{(P_C - P_T) - \delta(\Pi_C - \Pi_T)\}$$

Where J_V = net volume flow; K_F = filtration coeffi-

cient; P_C = intravascular hydrostatic pressure; P_T = interstitial hydrostatic pressure; δ = Staverman coefficient of reflectance; Π_C = capillary oncotic pressure; and Π_T = tissue oncotic pressure. P_C can be approximated from pulmonary capillary wedge pressure (PCWP) and Π_C is COP. The difference between P_C and Π_C defines the net force for fluid filtration from the intravascular space. Π_T and P_T are oncotic and hydrostatic forces in the interstitial space and cannot readily be measured in clinical studies. When Π_C decreases, or when the P_C increases, movement of fluid across capillary membranes to the extravascular space is favored. Normal values for P_C are in range of 10 to 15 mm Hg, whereas values for Π_C are in range of 18 to 20 mm Hg.

Although some authors have suggested that both lowered COP and lowered colloid osmotic pressure-pulmonary capillary wedge pressure gradient (COP-PCWP) are directly related to the development of pulmonary edema (3-7), these relationships have been questioned (2, 8-10). We studied the relationship of COP and COP-PCWP gradient to the development of

pulmonary insufficiency and overall mortality in critically ill patients in our Trauma and Surgical Intensive Care Units.

Methods and Materials

Between July 1977 and March 1978, 77 patients in the Trauma and Surgical Intensive Care Units were selected for study because they required flow-directed pulmonary arterial catheters for fluid management or treatment of respiratory insufficiency.

During the time of critical illness, daily measurements of COP by transducer membrane technique as described by Weil et al (3), PCWP, cardiac output (CO) by thermodilution technique, and arterial and mixed venous blood gas tensions were made. Intrapulmonary shunt ($\dot{Q}s/\dot{Q}t$) (11), left ventricular stroke work index (LVSWI), and COP-PCWP gradient were calculated from these measurements.

Patients were divided into survivors and nonsurvivors. These groups were compared with respect to age, lowest COP, lowest COP-PCWP, and LVSWI. Correlations between lowest COP and $\dot{Q}s/\dot{Q}t$ and between lowest COP-PCWP gradient and $\dot{Q}s/\dot{Q}t$ were determined. The magnitude of $\dot{Q}s/\dot{Q}t$ was used as a measure of pulmonary dysfunction and an indirect indication of the degree of fluid effusion in the lung. Data were analyzed using Student's t-test with statistical significance attributed to a p value less than 0.05.

Results

Of the 77 patients studied, there were 51 (66%) survivors and 26 (34%) nonsurvivors. Mean ages in years were 46 ± 3 (±SEM) and 58 ± 4, respectively ($p < 0.05$). The mean value for lowest COP was similar in survivors and nonsurvivors (Table 1). Nonsurvivors had a mean value of lowest COP-PCWP gradient significantly lower than did survivors (Table 1). At the point of lowest COP-PCWP gradient for each patient, COP was not significantly different between survivors and nonsurvivors, but PCWP was

significantly higher in nonsurvivors than in survivors (Table 2). LVSWI was significantly higher ($p < 0.01$) in survivors (52 ± 2 g·m/m^2) than in nonsurvivors (44 ± 3 g·m/m^2). The mean $\dot{Q}s/\dot{Q}t$ at lowest COP and at lowest COP-PCWP was not significantly different between the groups (Table 3).

No correlation was found between $\dot{Q}s/\dot{Q}t$ and lowest COP in nonsurvivors or in survivors (Fig 1). In addition, lowest COP-PCWP gradient in the overall study did not correlate with $\dot{Q}s/\dot{Q}t$ (Fig 2). None of the 26 nonsurvivors had progressive respiratory insufficiency as the primary cause of death.

Discussion

Colloid osmotic pressure and COP-PCWP gradient have been correlated with mortality and the development of pulmonary insufficiency by various observers. Tonnesen and colleagues (7) showed that lowered COP correlated closely with elevated mortal-

TABLE 2

COP and PCWP at Lowest COP-PCWP Gradient*

	Survivors	Nonsurvivors	p value
COP (torr)	15 ± 1	15 ± 1	NS
PCWP (torr)	12 ± 1	16 ± 1	<0.01

* Values are means ± SEM.

TABLE 3

Intrapulmonary Shunt ($\dot{Q}s/\dot{Q}t$) at Lowest COP and at Lowest COP-PCWP Gradient in Survivors and Nonsurvivors*

	Survivors	Nonsurvivors	p value
$\dot{Q}s/\dot{Q}t$ at lowest COP (%)	18 ± 1	20 ± 1	NS
$\dot{Q}s/\dot{Q}t$ at lowest COP-PCWP (%)	18 ± 1	21 ± 1	NS

* Values are means ± SEM.

TABLE 1

Lowest Colloid Oncotic Pressure (COP) and Lowest Colloid Oncotic Pressure-Pulmonary Capillary Wedge Pressure (COP-PCWP) Gradient in Survivors and Nonsurvivors*

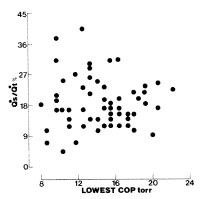|	Survivors	Nonsurvivors	p value
Lowest COP (torr)	15 ± 1	14 ± 1	NS
Lowest COP-PCWP (torr)	3 ± 1	−1 ± 2	<0.05

* Values are means ± SEM.

FIG 1. Lack of relationship between lowest COP and $\dot{Q}s/\dot{Q}t$ in 77 critically ill surgical patients.
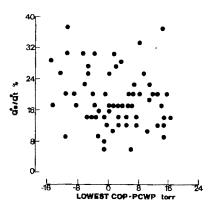
FIG 2. Absence of correlation between lowest COP-PCWP and Qs/Qt in total group of patients.

ity, although this relationship was independent of respiratory insufficiency. Rackow et al (4) found that lowered COP-PCWP gradient was closely associated with the development of pulmonary edema. Rackow et al reported that all of the patients who had myocardial infarction and a COP-PCWP gradient of less than 4 mm Hg also had pulmonary edema. Rackow and associates also showed a marked reduction in survival associated with a lowered COP. Weil and co-workers (6) have also shown a correlation between lowered COP and mortality. In addition, they demonstrated a correlation between lowered COP-PCWP gradient and the development of pulmonary edema as measured by chest roentgenography. The wide range of variability in the interpretation of chest roentgenograms makes this determination difficult to quantify as a clinical measurement.

Use of arterial and venous blood gas measurements to calculate Qs/Qt provides a more precise index of pulmonary insufficiency than physical examination of radiographic evidence of pulmonary edema (12–15) and, therefore, we chose it as the basis for comparison in this study. Many authors (3–7) have shown a correlation between COP-PCWP gradient and radiographic evidence of pulmonary edema, but did not attempt to correlate these parameters with Qs/Qt. Intrapulmonary shunt is an objective sensitive measurment of lung function. Pulmonary edema results in an increase in Qs/Qt. Intrapulmonary shunt is felt to increase as lung water accumulates. Changes in Qs/Qt often occur before there are changes in the chest radiograph indicative of pulmonary edema.

We found that the lowest COP was not significantly different in survivors and nonsurvivors. Lowest COP-

PCWP gradient was lower in the nonsurvivors, suggesting that myocardial function had an impact on survival. We found no correlation between the lowest COP or lowest COP-PCWP and Qs/Qt. These observations suggest that COP and PCWP are not the critical factors in predicting the degree of respiratory insufficiency or likelihood of survival in critically ill surgical patients. The Starling hypothesis remains a complex relationship which will continue to require careful clinical study and application in order to be understood.

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Varying Electrical Acupuncture Stimulation Intensity: Effects on Dental Pain-Evoked Potentials

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Electrical acupunctural stimulation (EAS) has repeatedly been shown in the laboratory to diminish human dental pain perception. This study compared the effects of low, medium, and high EAS levels on event-related potentials elicited by painful dental stimulation and on subjective pain report. Acupuncture was performed bilaterally at LI-4 on the hands, and each subject received all EAS levels, counterbalanced for order. Only the highest level of EAS was effective, and it reduced the pain report in addition to the amplitudes of the positive event-related potential deflections from base line at 100 and 250 msec. No dose-response effect was observed for EAS levels. The outcome suggests that the analgesic effect occurs abruptly when stimulation reaches a strong level and a subnoxious pounding sensation is elicited.

ALTHOUGH the analgesic effects of electrical acupuncture stimulation (EAS) have been reported in several studies from laboratories where dental dolorimetry has been used to elicit laboratory pain (1–4), only minimal information has been provided about the role of stimulation intensity in the induction of analgesia. To increase dental pain threshold with acupuncture, Andersson and Holmgren (1) found it necessary to induce a strong pounding sensation at the site of the needle by using a subjectively high (EAS) intensity. Chapman and colleagues (2, 5) repeatedly observed that electrical acupuncture reduced dental perceptual capability (d′) in sensory decision theory studies when stimulus intensity was strong but did not exceed the comfort level of the subject. Recently, they showed (6) that EAS can alter brain-evoked potential amplitudes elicited by painful tooth pulp stimulation when stimulation is strong.

Dental event-related potential (ERP) amplitudes have correlated well with changes in pain perception as stimulus intensity varies (7, 8). Moreover, analgesic treatments which decrease pain perception also diminish ERP amplitudes. For example, Chapman and associates have observed that ERP amplitudes decrease following treatment with aspirin, 975 mg (9), fentanyl, 0.1 mg IV (10), nitrous oxide 33% inhaled in oxygen (11), and lidocaine 2% infiltration of the soft tissues at the apex of the tooth being tested (12). Recently Buchsbaum et al (13) reported similar changes in the ERP elicited by painful electrical cutaneous stimulation when aspirin, 1.0 g, and morphine, 5.0 mg, were given. As EAS appears to alter brain response to painful dental stimulation much the same as other analgesics, it is of interest to determine whether its dosage can be varied.

In this study three different EAS intensities were given to subjects in order to determine whether a relationship exists between intensity of the stimulation delivered through the needles and the dental analgesic effect of acupuncture. It was hypothesized that small, medium, and high stimulation intensities would result in three gradients of ERP modulation, thus demonstrating a dose-response relationship between electrical stimulation intensity and analgesic effect.

Method

Subjects

Twelve paid volunteers ranging in age from 21 to 31 years were involved in the study. Each filled out a health questionnaire and signed a consent form approved by the University of Washington Human Subject Research Committee.

Dolorimetry

For each subject a healthy, unfilled, central incisor was stimulated via a 3.5-mm conductive rubber electrode (cathode) mounted in a plastic shaft and held against the subject's tooth by one of the experimenters. Quality of the contact between the stimulating cathode and tooth was ensured by continued observance of a digital resistance meter. The anodal electrode was taped to the left zygomatic arch. Stimuli were generated by a Grass S-44 stimulator and controlled by constant current and stimulus isolation units. Stimulus intensity was determined by display of the 5-msec square wave pulses on a calibrated oscilloscope. These pulses ranged in intensity from 10 to 80 μamp depending on the subject, with a mean intensity of 66 μamp. In order to select a suitable dental stimulus level for each subject at the outset, stimuli were given repeatedly with small increments in intensity until a level judged as strong or moderate pain was obtained. During actual testing the stimuli were presented every 2 seconds at this level. A detailed description of the dental dolorimetry system used has been provided by Martin and Chapman (14).

ERP Recording

A 600-msec epoch of electrical brain activity was sampled on each trial beginning 100 msec before the delivery of the dental stimulus. Samples were recorded from vertex (Cz) referred to occiput (Oz) with the zygomatic arch as ground, and electrode resistances were maintained at less than 5 kohm. Each testing session lasted 1.5 to 2.0 hours. Signals were amplified via a model 277J Analog Devices isolation unit with an effective band width of 0.2 to 100 Hz (3 dB down) and the signal from Op-Amp was fed directly into a Nicolet 1072 signal averager. The input of the Nicolet digitizer (SD72/4A) was set to a time constant of 4 msec with a sampling rate of 800 Hz. The signal averaging process was monitored on an oscilloscope.

Each measure obtained was derived from a summation average for 192 trials produced by summing three averages, each from 64 repeated presentations of identical dental stimuli. To guard against possible artifacts caused by alpha rhythm, neck muscle tension, eyeblinks, or ocular rotation, the consistency of each set of three 64-trial averages was assessed, and atypical recordings were discarded and replaced.

The ERP wave form data were quantified in terms of the base-to-peak amplitudes and peak latencies at each of the major deflections from base line, identified here in terms of polarity (N, negative; P, positive) and peak latency in milliseconds. Peak latencies and amplitudes for each 192-trial average obtained were digitized and submitted to analysis.

The pain ratings, scored 1 to 6, were derived from verbal reports based on a scale of six categories: 1, very faint sensation; 2, very faint pain; 3, faint pain; 4, mild pain; 5, moderate pain; and 6, strong pain. These ratings were obtained at the end of each block of 192 trials.

After the base line ERPs were obtained electrical acupuncture was delivered bilaterally via sterile needles inserted approximately 1.5 cm at LI-4 on the dorsal aspect of the hand between the first and second metacarpal bones near the radial side of the middle of the second metacarpal. A Sanyo Denshi SD207 stimulator was used to deliver biphasic wave forms at 2 Hz from two output ports. On each of the subject's hands the cathode was connected to the acupuncture needle and the anode was taped to the palmar surface of the index finger.

Stimulation levels given to each subject were individually determined before the attempt to induce analgesia commenced. The output voltage of the stimulator was increased slowly to an intensity at which the subject detected a distinct pulsing sensation. This voltage was recorded and designated as low intensity stimulation. High intensity stimulation was defined by further increasing the voltage to the highest possible non-noxious level. The average of the low and high voltages was defined as the medium intensity. Mean voltages across subjects for the three EAS levels were 0.57, 2.05, and 3.43 V. Each level of stimulation was applied for 20 minutes before the ERPs were recorded.

Design

The order of the three stimulation intensities was counterbalanced across subjects. This formed six groups of two subjects each. Data were statistically analyzed by mixed design analysis of variance with order as a grouping variable and acupuncture stimulation intensity as a within-subjects variable.
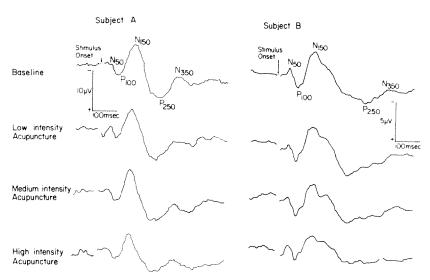
Subject A

Subject B

Baseline

Low intensity
Acupuncture

Medium intensity
Acupuncture

High intensity
Acupuncture

FIG 1. Event-related potential (ERP) wave forms for two representative subjects are presented across base line and three treatment levels. Each wave form is a 192-trial summation average recorded at vertex with reference to inion. Base lines were estimated from 100-msec prestimulus average and used to calculate base-to-peak amplitudes.

Results

In addition to subjective report the ERP wave forms yielded five base-to-peak amplitude scores and five peak latencies as shown in Fig 1 in which wave forms for two subjects are presented across base line and three EAS levels. To reduce the number of data points entered into univariate statistical analyses, we examined the correlation of EAS level (dosage) with each of the dependent variables and selected only those measures whose correlations with dosage were greater than $r = 0.20$. With this criterion subjective pain report (SPR), P100 amplitude (P100 AMP), and P250 amplitude (P250 AMP) were selected for analysis of variance procedures. The outcomes of the analyses of variance are shown in Table 1, and Fig 2 displays the mean change in ERP and SPR variables across dosage levels. Dunnett's test (15) was used for a posteriori testing of each of the values against the base line measure.

A significant dosage effect was seen with P100 AMP, P250 AMP, and SPR, but a posteriori tests revealed that this effect occurred only with the highest stimulus intensity (see Fig 2). Thus, the acupuncture effect occurred on an "all-or-nothing" basis when stimulus intensity reached an adequate level.

In Table 2 are presented the correlations between the independent variables (dosage and order) and the dependent variables (P100 AMP, P250 AMP, and SPR). Interestingly, there was a substantial relationship between order of treatment and both P250 AMP and SPR measures but not between the P100 AMP

TABLE 1

Analysis of Variance Summarized for P100 Amplitude (P100 AMP), P250 Amplitude (P250 AMP), and Subjective Pain Report (SPR)

Source	Sum of squares	df	Mean square	F	p
P100 AMP					
Order (O)	3.999	5	0.800	0.19	0.958
Dose (D)	6.228	3	2.076	5.76	0.006
Subject (O)	25.86	6	4.311		
O × D interaction (SD)	8.591	15	0.573	1.59	0.173
SD (O)	6.487	18	0.360		
P250 AMP					
Order (O)	121.403	5	24.281	0.82	0.576
Dose (D)	26.275	3	8.758	3.23	0.047
Subject (O)	177.169	6	29.538		
O × D interaction (SD)	31.038	15	2.069	0.76	0.699
SD (O)	8.840	18	2.713		
SPR					
Order (O)	19.167	5	3.833	5.75	0.028
Dose (D)	2.292	3	0.764	6.11	0.005
Subject (O)	4.000	6	0.667		
O × D interaction (SD)	1.458	15	0.972	0.78	0.686
SD (O)	2.250	18	0.125		

and order. To further evaluate the treatment effect, a multiple regression was performed in which the dependent variable or criterion was dosage and the four independent variables, or predictors, were P100 AMP, P250 AMP, SPR, and order of treatment. This resulted in the multiple regression coefficient, $r = 0.395$, and the square of this number, 0.156, indicated the proportion of variance explained by these four variables. As ERP, SPR, and the order variable accounted for only approximately 16% of the variance in the data, the treatment effect was rather weak even though it was statistically significant. This occurred because
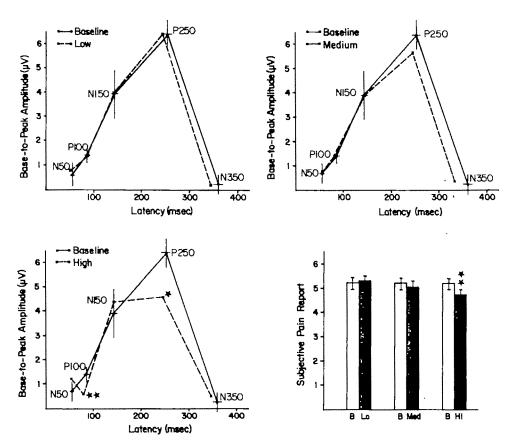
FIG 2. Effects of electrical acupunctural stimulation (EAS) levels on mean (±1 SEM) ERP and subjective pain report (SPR) scores. ERP data are plotted as deviation from base line (absolute value) over time. Area under function thus defined indicates

electrical energy expended by brain over 500 msec in processing tooth pulp stimulus. Statistical significance for a posteriori tests is indicated: ★ = $p < 0.05$, ★★ = $p < 0.01$.

TABLE 2

Correlations among Dependent Measures, and Order of Treatment for Electrical Acupunctural Stimulation (EAS) Intensity Levels (Dose)

	Order	P100 AMP	P250 AMP	SPR	Dose
Order	1.000				
P100 AMP	0.055	1.000			
P250 AMP	0.271	0.229	1.000		
SPR	0.302	0.089	0.331	1.000	
Dose	−0.000	−0.300	−0.259	−0.212	1.000

suboptimal stimulation intensities were used at the low and medium levels, and an effective stimulation level was used only while testing at the highest intensity.

Discussion

The data demonstrate that low intensities of acupunctural stimulation are ineffectual in establishing dental analgesia in human laboratory volunteers undergoing painful tooth pulp stimulation. A dose-response effect was not observed, and it seems clear from the statistical analyses that the analgesic effect

occurs abruptly as acupunctural stimulation intensity is increased, beginning at the point where a strong pounding sensation is obtained. Our data do not preclude the possibility that a dose-response curve could be demonstrated if several very high EAS intensities were used. Unfortunately, this is difficult, if not impossible, to test in human volunteers as it would require stimulation at extremely noxious and perhaps intolerable levels.

Also contributing to the small treatment effect observed was the use of central incisors for the tests. Janhunen and Närhi (3) as well as Mattila, Ketovuori, and Pöentinen (4) found that dental acupuncture analgesia, obtained by stimulation at LI-4, was smallest at the incisors and increased in depth as they moved back through premolars to the molars. It is likely that the effect reported here would have been more profound if molar teeth were tested.

Finally, the data thus far available suggest that the outcomes of studies such as this one, which examine the ability of EAS treatments to block pain in a healthy volunteer, may not generalize easily to the

clinical application of EAS therapy for the patient with chronic pain. Andersson and Holmgren (1), for example, reported that low frequency stimulation worked best for laboratory EAS modulation of pain, but higher stimulation frequencies (>100 Hz) were more effective for chronic pain alleviation. Clearly, more information is needed about stimulation frequency and intensity before a conclusion can be reached, and clinicians should proceed cautiously in building a knowledge base for EAS pain therapy from the experimental literature.

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Changing Specialties: Do Anesthesiologists Differ from Other Physicians?

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SELTZER, J. L., AND VELOSKI, J.: Changing specialties: do anesthesiologists differ from other physicians? Anesth Analg 1982;61:504-6.

Career choices of physicians frequently change after senior year in medical school. Although previous studies have documented the magnitude of these changes, they contain no information concerning anesthesiologists. Changes in specialties of 1151 physicians, graduates from the same medical school, between the years 1968 and 1976 were studied. Of these physicians, 35 (3%) are presently engaged in the practice of anesthesiology. Of 31 physicians who planned careers in anesthesiology as seniors, 26 (84%) remained in anesthesiology. Nine physicians changed from other specialties to anesthesiology. The ability of anesthesiology to retain physicians who originally planned to specialize in it, or to gain physicians from other fields, was not different from that found in other specialties studied.

Key Words: MANPOWER; EDUCATION: medical students.

MATTESON and Smith (1), in a study of career choices of medical students, found a difference between the specialty that senior medical students said they would like to be in (their preferred specialty) and the specialty they actually planned to enter (their chosen specialty). Nearly one quarter of all students indicated they chose to enter a specialty other than that which would be their first preference. Reasons given for this difference included: a low demand for their preferred specialty, the nature of training in their preferred specialty, too much time demanded by their preferred specialty, the feeling that they lacked the required ability for their preferred specialty, the feeling that their preferred specialty required too much responsibility, they did not care for the people already in their preferred specialty, the belief that their preferred specialty lacked prestige, the feeling that it would be too difficult to get a residency in their preferred specialty, they did not like the type of patient they would deal with in their preferred specialty, the feeling that their preferred

specialty offered no challenge, or the feeling that their preferred specialty was inconsistent with their personality. The choices of specialties offered in the questionnaire used by Matteson and Smith were internal medicine, surgery, psychiatry, pediatrics, obstetrics-gynecology, general practice, or "others." Because anesthesiology was included in "others," no useful information could be gathered concerning the specialty.

Not only do physicians enter specialties that are not their prime preference, they also may change specialties after some training in their field of first preference. Wasserman and colleagues (2) followed one medical school class from their freshman year through their 7th postgraduate year. They reported that half of the medical students changed specialty choice between freshman and senior years and that after graduation 23% changed specialties by the 5th postgraduate year. Of the 58 physicians followed, only two were anesthesiologists, thus it was difficult to apply their data to our specialty.

More recently, Holden and Levit (3) reported on a longitudinal study of graduates of medical schools in the United States. They randomly selected 10% of the graduating classes of 1960, 1964, and 1968. There were 664 physicians in the 1960 cohort, 673 in the 1964 cohort, and 709 in the 1968 cohort, totaling 2046. They examined how many of these physicians changed specialties in the years 1971 through 1976. The most recent graduating class had the largest

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percentage of physicians changing fields; 29% in the class of 1968, 11% in the class of 1964, and 8% in the class of 1960. The specialties analyzed included internal medicine, pediatrics, family practice, obstetrics-gynecology, medical subspecialties, surgical subspecialties and other. Anesthesiology was included in the other category along with dermatology, pathology, physical medicine, preventive medicine, psychiatry, neurology, and radiology. It is difficult to draw any conclusions concerning anesthesiology from these data. We undertook a study to document the magnitude of change of anesthesiologists into and out of our specialty.

Methods

Data for the present study were derived from a longitudinal study of medical students and graduates conducted at the Jefferson Medical College since 1968 (4, 5). Each year a questionnaire was administered to senior students approximately 1 hour before they received the results of the matching program for residency training (internships in earlier years). One item in the questionnaire asked the senior about the type of residency training planned after the 1st year of postgraduate training. Senior questionnaires were available for 1306 (78%) of 1676 graduates from classes graduating in the years 1968 through 1976, inclusive.

The actual current specialties of Jefferson graduates were subsequently obtained five or more years after graduation from the alumni office of the college. The actual specialty for 155 of the graduates in the time period could not be obtained from the records of the alumni office because the graduate had either not completed training, was not actively practicing, or, in a few cases, was deceased. The remaining 1151 (69%) graduates were classified into 11 large specialty groupings and one other group which included small numbers of graduates in programs such as ophthalmology, otolaryngology, and preventive medicine.

The plans for specialization and actual specialties were cross tabulated, and the proportion of graduates remaining in their planned specialties was calculated. The proportions were compared using the Z test for proportions.

Results

Of the 1151 graduates 35 (3%) listed anesthesiology as their present specialty. Of the 31 students who planned to go into anesthesiology as seniors, 26 actually did so, an 84% retention rate. Nine physicians changed from other specialties into anesthesiology,

TABLE 1

Career Choices of Senior Medical Students and Eventual Areas of Practice

Specialty	No. of seniors planning to enter each specialty	No. of seniors actually entering each specialty	% retained*
Anesthesiology	31	26	84
Family medicine	138	105	76
Internal medicine	351	312	89
Obstetrics-gynecology	77	61	79
Orthopedics	64	44	69
Pathology	33	26	79
Pediatrics	83	70	84
Psychiatry	60	50	83
Radiology	46	31	67
Surgery	153	110	72
Urology	24	15	63
Other	91	70	77

* Percentage retained = (number retained)/(number planned) × 100.

TABLE 2

Career Changes after Graduation

Specialty	No. retained*	No. gained	% gained†	No. actually in field
Anesthesiology	26	9	26	35
Family medicine	105	36	26	141
Internal medicine	312	73	19	385
Obstetrics-gynecology	61	12	16	73
Orthopedics	44	4	8	48
Pathology	26	5	16	31
Pediatrics	70	14	17	84
Psychiatry	50	10	17	60
Radiology	31	14	31	45
Surgery	110	23	17	133
Urology	15	5	25	20
Other	70	26	27	96

* Number of physicians in each specialty who planned to enter that specialty as senior medical students (Table 1).

† Percentage gained = (number gained)/(number in specialty) × 100.

representing a 26% gain. In Tables 1 and 2 the results for the different specialties are compared. The percentage of students remaining in their planned specialties ranged from 89% for internal medicine to 63% for urology. Radiology had the highest percent gained (31%). Anesthesiology and family medicine were third highest with 26% gained. However, there were no statistically significant differences between any of the specialties examined in their ability to retain or gain physicians.

Discussion

In the present study involving eight medical school classes followed for 5 to 13 years, 20% of physicians

changed specialties following graduation. This is in agreement with Wasserman's figure of a 23% change in the first 5 postgraduate years (2). The data of Holden and Levit (3) indicated that 29% of physicians changed their specialties in their first 8 postgraduate years. Their percentage of physicians changing specialties is higher because they included changes from a specialty to a subspecialty in the same field as well as changes to a completely different field. For example, a physician who was listed as an internist and now limits his practice to cardiology would have been considered to have changed his field by Holden and Levit but not by us.

The fact that at least 20% of medical graduates change specialties raises some interesting questions. Does it result from medical students electing fields to which they have been inadequately exposed in medical school? If so, then students should be encouraged to learn more about possible career choices by means of additional elective time before graduation. On the other hand, the medical school students may not have received enough or the correct type of exposure to the field they ultimately select. If this is true, then a more general medical school education, which would provide better exposure to all fields of medicine, is needed.

It is interesting to note that in our study all physicians leaving anesthesiology entered either internal medicine or family practice. All those who entered anesthesiology after graduation came from surgical fields. The numbers involved are probably too small to be of significance but the entry into anesthesiology from surgical fields is understandable because of the exposure of surgical house officers to anesthesiology.

Both Wasserman and colleagues (2) and Holden and Levit (3) demonstrated an increasing stability in

specialty choices with the length of time after graduation from medical school. This is understandable in that the longer a physician stays in a residency or a practice, the greater his understanding of what is demanded by that field and his compatibility with that specialty. Also, with the magnitude of financial indebtedness of many of today's graduates, the need to enter practice to repay loans may preclude "starting over" in a new residency after several years have been spent in another field.

For whatever reasons physicians change specialties, anesthesiology does not appear to be different from other specialties in its ability to retain or gain physicians. If medical school exposure is important, our data indicate that our curriculum, which includes a 2-week required clerkship and the possibility of a 1-month elective, is adequate. Other specialties to which students have much greater exposure seemed to gain and lose physicians at the same rate as anesthesiology. It must be remembered that our data represent only one medical school. If students received different types or amounts of formal training in anesthesiology, there could be a greater number of physicians changing into or out of anesthesiology.

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One-Lung Anesthesia: Percent Shunt and Arterial Oxygen Tension during Continuous Insufflation of Oxygen to the Nonventilated Lung

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REES, D. I., AND WANSBROUGH, S. R.: One-lung anesthesia: percent shunt and arterial oxygen tension during continuous insufflation of oxygen to the nonventilated lung. Anesth Analg 1982;61:507-12.

Twenty-four male patients scheduled for elective pulmonary resection were studied to determine whether continuous insufflation of oxygen to the nonventilated lung would reduce intrapulmonary shunting ($\dot{Q}_s/\dot{Q}_t$) and arterial oxygen desaturation. Measurements of physiologic variables were made using pulmonary arterial and peripheral arterial catheters. Blood was sampled for analysis and $\dot{Q}_s/\dot{Q}_t$ and other hemodynamic variables were calculated. Significant differences were observed in $\dot{Q}_s/\dot{Q}_t$ and arterial oxygen tensions (Pa_{O_2}) between patients in whom oxygen was insufflated and those in whom oxygen was not insufflated. Patients with oxygen insufflation had significantly lower $\dot{Q}_s/\dot{Q}_t$ and consistently higher Pa_{O_2}. Statistically significant differences in $\dot{Q}_s/\dot{Q}_t$ became apparent after 15, 30, and 45 minutes of one-lung ventilation compared with values for patients not receiving oxygen insufflation. Six of 12 patients without oxygen insufflation had peak $\dot{Q}_s/\dot{Q}_t$ levels greater than 50%, whereas none of the patients in whom oxygen was insufflated had levels that exceeded this amount. Of 12 patients given oxygen insufflation, one had a Pa_{O_2} of less than 100 torr at the point of maximum decrease in arterial oxygen tension, compared with six of 12 patients in whom oxygen was not insufflated. These findings suggest that continuous oxygen insufflation of the nonventilated lung during periods of one-lung ventilation reduces $\dot{Q}_s/\dot{Q}_t$ and minimizes arterial oxygen desaturation.

Key Words: ANESTHETIC TECHNIQUES: endobronchial; LUNG: shunting.

A RTERIAL oxygen desaturation and increasing intrapulmonary shunting occur during periods of one-lung ventilation (OLV) (1). Various techniques aimed at improving arterial oxygenation and reducing intrapulmonary shunting during OLV have been investigated. These range from positive end-expiratory pressure (PEEP) to the dependent ventilated lung (2–4) to oxygen insufflation together with PEEP to the upper nonventilated lung (5).

Although Churchill-Davidson (6) recommended insufflation of the affected lung during periods of collapse to diminish hypoxemia, no study to date has conclusively investigated the potential beneficial effects of continuous insufflation of oxygen without PEEP to the nonventilated lung during OLV. We investigated this technique by comparing one group of patients having thoracotomies with a period of OLV with a second group not having oxygen insufflation to the nonventilated lung.

Methods

Twenty-four male patients undergoing elective lung resections for carcinoma were studied. Institutional approval of the study and informed consent were obtained. The patients were distributed into two groups according to a computer-generated randomization schedule. Two other patients were removed from the study because insufficient data were obtained due to the brevity of the period of OLV.

Clinical history and preoperative laboratory data were collected for all patients. Premedication consisted of diazepam, 10 mg, given 90 minutes before arrival in the operating room and Innovar (2 ml) given intravenously before insertion of monitoring lines. Anesthesia was induced with thiopental, 3 to 4 mg/kg, with pancuronium, 0.1 mg/kg, used to facilitate

intubation. Maintenance of anesthesia was achieved with enflurane 1% to 2% in oxygen. All patients had large Robertshaw double-lumen endobronchial tubes to provide lung separation and to facilitate OLV. The Ohio fluidically operated anesthesia ventilator was used to provide mechanical ventilation at a volume of 12 ml/kg/breath, at a rate of 10 breaths per minute. These settings remained unaltered throughout the operative period with attention directed toward ensuring that peak airway pressure did not exceed 30 torr following the changeover from two- to one-lung ventilation. Separation of ventilation was verified by auscultation in the prone and lateral positions before commencement of surgery. During the period of OLV, one group of patients received continuous insufflation of oxygen at a rate of 1 L/min via a #14

French bronchial catheter, introduced 7.5 to 10 cm into the nonventilated side of the Robertshaw tube, without occluding the lumen of the endobronchial tube. In patients in whom oxygen was not insufflated, the nonventilated side remained open to atmosphere.

Before induction of anesthesia, a 20-gauge, 5-cm Abbocath was inserted into the dependent radial artery under local analgesia, and a Swan-Ganz 7 French triple-lumen thermodilution catheter was placed in the pulmonary artery via the internal or external jugular vein after lidocaine infiltration. Intravascular pressures and the electrocardiogram (ECG) were monitored using the Tektronix 414 with option 21 and alpha-numeric strip recorder output. Preinduction readings and blood samples were taken with the patient in the supine position and breathing room air. Initial base line readings and blood samples were taken 15 minutes after the patient was placed in the lateral position and before OLV. Subsequent readings and blood samples were taken at 5, 15, 30, and 45 minutes after establishing OLV and 15 minutes following termination of OLV. Each set of data included heart rate, mean systemic and pulmonary arterial pressures (MAP and MPAP), mean pulmonary arterial wedge pressure (PAWP), central venous pressure (CVP), and percent enflurane administered. After ensuring a good pulmonary artery wave form, mixed venous blood samples and systemic arterial blood samples were drawn for measurements of blood gas tensions and pH. Samples were packed in ice and analyzed within 5 minutes of being drawn using the Corning pH/blood gas 165 machine. Repeated calibrations were performed and only minor adjustments needed to adjust the machine correctly to the values of standards internal to the instrument (coefficients of variation of the P_{O_2} electrode over the following ranges were: 40 to 80 torr = 15%, 90 to 110 torr = 2%, 140 to 150 torr = 1%, >150 torr = <1%). Cardiac output was determined using the thermodilution technique (mean of three measurements) and Edwards Laboratories' cardiac output computer model 9520A which also recorded blood temperature.

Following temperature correction of P_{aO_2}, using the Kelman and Nunn Temperature Correction Chart, and alveolar water vapor pressure the following calculations were made using an Apple 11 computer and standard formulas: intrapulmonary shunt ($\dot{Q}_s/\dot{Q}_t$), cardiac index, left ventricular stroke work index (LVSWI), oxygen consumption ($\dot{V}_{O_2}$), oxygen delivery, pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR).

The above mentioned data were statistically ana-

EQUATIONS

Shunt equation	$\dfrac{\dot{Q}_s}{\dot{Q}_t} = \dfrac{Cc'_{O_2} - Ca_{O_2}}{Cc'_{O_2} - C\bar{v}_{O_2}} \times 100$	
Cc'_{O_2}	=	$(P_{AO_2}(0.0031)) + (Hb \times 1.34)$
P_{AO_2} (on air)	=	$(P_B - P_{H_2O}) \cdot F_{IO_2} - (Pa_{CO_2}/0.8)$
P_{AO_2} (100% O_2)	=	$P_B - Pa_{CO_2} - P_{H_2O} - P_{Eth}$
Ca_{O_2}	=	$(Pa_{O_2}(0.0031)) + (Hb \times 1.34 \times Sat/100)$
$C\bar{v}_{O_2}$	=	$(P\bar{v}_{O_2}(0.0031)) + (Hb \times 1.34 \times Sat/100)$
Cardiac index (CI)	=	$\dot{Q}_t$/body surface area
O_2 consumption ($\dot{V}_{O_2}$)	=	$\dot{Q}_t \times C(a-\bar{v})_{O_2} \times 10$
O_2 delivery	=	$Ca_{O_2} \times CI \times 10$
SVR	=	$(MAP - CVP)/CI$
PVR	=	$(MPAP - PAWP)/CI$

ABBREVIATIONS

FVC	forced vital capacity
FEV_1	forced expired volume in 1 second
OLV	one-lung ventilation
MAP	mean systemic arterial pressure
MPAP	mean pulmonary arterial pressure
PAWP	pulmonary arterial wedge pressure
CVP	central venous pressure
$\dot{Q}_t$	cardiac output
$\dot{Q}_s/\dot{Q}_t$	percent shunt
$\dot{V}_{O_2}$	oxygen consumption
LVSWI	left ventricular stroke work index
PVR	pulmonary vascular resistance
SVR	systemic vascular resistance
Pa_{O_2}	arterial oxygen tension
Pa_{CO_2}	arterial carbon dioxide tension
$P\bar{v}_{O_2}$	mixed venous oxygen tension
F_{IO_2}	fraction inspired oxygen
$\dot{V}/\dot{Q}$	ventilation-perfusion ratio
HPV	hypoxic pulmonary vasoconstriction

lyzed using the repeated measures analysis of variance technique with one grouping variable and six repeated measures for analysis of interaction, group effect, and time effect. In the presence of interaction, the data obtained were further analyzed using the Newman-Keuls multiple comparison technique to determine whether differences between the two groups were statistically significant (7).

Results

Patients were divided into two groups: those receiving oxygen insufflation (group 1) and those not receiving insufflation (group 2). Both groups had mean ages of 56 $\pm$ 19 (SD) years. Smoking history was similar in both groups: patients in group 1 had a mean of 66 $\pm$ 34 pack years (packs per day $\times$ number of years smoked) and those in group 2 a mean of 63 $\pm$ 44 pack years. Preoperative pulmonary function tests showed patients in group 1 to have a forced vital capacity (FVC) mean of 3.21 $\pm$ 1.3 L and a mean forced expiratory volume in 1 second (FEV_1) of 1.89 $\pm$ 0.76 L. Patients in group 2 had a mean FVC of 3.41 $\pm$ 1.3 L and a mean FEV_1 of 2.15 $\pm$ 0.99 L. Preinduction

values for Pa_{O_2}, Pa_{CO_2}, $P\bar{v}_{O_2}$, and $\dot{Q}_s/\dot{Q}_t$ in both groups with the patients in the supine position and breathing room air, were also similar (Tables 1 and 2). Six right-sided thoracotomies and six left-sided thoracotomies were performed in each group, all with lobectomies.

The collected and derived data obtained for each group are shown in Tables 1 and 2. $\dot{Q}_s/\dot{Q}_t$ and Pa_{O_2} were plotted against time (Figs 1 and 2) and clearly show the difference between the two groups. Histograms of the results (Figs 3 and 4) illustrate that with respect to $\dot{Q}_s/\dot{Q}_t$, 50% of the patients in group 2 (non-insufflated) had peak $\dot{Q}_s/\dot{Q}_t$ greater than 50% whereas none of the patients in group 1 (insufflated) had peak $\dot{Q}_s/\dot{Q}_t$ greater than 50%. Conversely, 75% of patients who had oxygen insufflation of the nonventilated lung during OLV had peak $\dot{Q}_s/\dot{Q}_t$ less than 35% whereas only 25% of patients without oxygen insufflation had peak $\dot{Q}_s/\dot{Q}_t$ in that range. Six of 12 patients in group 2 (non-insufflated) had minimum Pa_{O_2} levels of less than 100 torr during the period of OLV. Only one of 12 patients in whom oxygen was insufflated had a minimum Pa_{O_2} of less than 100 torr.

The $\dot{Q}_s/\dot{Q}_t$ in both groups increased with time on OLV. Statistical analysis of this index using the re-

TABLE 1

Group 1: 12 Patients with Continuous Oxygen Insufflation*

Index	Time with insufflation					
	15 min (2 lungs)	5 min (1 lung)	15 min (1 lung)	30 min (1 lung)	45 min (1 lung)	15 min (2 lungs)
$\dot{Q}_s/\dot{Q}_t$ (%)	17 $\pm$ 4	23 $\pm$ 4	29 $\pm$ 6	30 $\pm$ 8	31 $\pm$ 5	21 $\pm$ 6
Pa_{O_2} (torr)	411 $\pm$ 57	348 $\pm$ 76	254 $\pm$ 102	231 $\pm$ 125	206 $\pm$ 76	350 $\pm$ 104
Pa_{CO_2} (torr)	37 $\pm$ 5	38 $\pm$ 6	37 $\pm$ 6	37 $\pm$ 5	39 $\pm$ 7	38 $\pm$ 8
$P\bar{v}_{O_2}$ (torr)	52 $\pm$ 6	60 $\pm$ 12	54 $\pm$ 10	54 $\pm$ 13	52 $\pm$ 12	55 $\pm$ 11
$\dot{V}_{O_2}$ (ml/min/m²)	103 $\pm$ 16	96 $\pm$ 16	98 $\pm$ 19	99 $\pm$ 21	95 $\pm$ 15	103 $\pm$ 14
Cardiac index (L/min/m²)	2.74 $\pm$ 0.65	3.09 $\pm$ 0.64	2.93 $\pm$ 0.55	2.98 $\pm$ 0.75	2.86 $\pm$ 0.66	2.84 $\pm$ 0.63
PVR (torr·min·m⁻⁵)	2.51 $\pm$ 0.84	2.52 $\pm$ 0.75	2.79 $\pm$ 1.14	3.02 $\pm$ 1.03	2.70 $\pm$ 0.47	2.30 $\pm$ 0.89
Heart rate (beats/min)	76 $\pm$ 15	85 $\pm$ 12	87 $\pm$ 14	87 $\pm$ 16	86 $\pm$ 19	79 $\pm$ 13

* Values are means $\pm$ SD. Abbreviations used are: 2 lungs, both lungs ventilated; 1 lung, only dependent lung ventilated.

TABLE 2

Group 2: 12 Patients without Oxygen Insufflation*

Index	Time without insufflation					
	15 min (2 lungs)	5 min (1 lung)	15 min (1 lung)	30 min (1 lung)	45 min (1 lung)	15 min (2 lungs)
$\dot{Q}_s/\dot{Q}_t$ (%)	18 $\pm$ 5	30 $\pm$ 8	39 $\pm$ 15	43 $\pm$ 15	42 $\pm$ 13	25 $\pm$ 7
Pa_{O_2} (torr)	383 $\pm$ 56	274 $\pm$ 97	181 $\pm$ 103	145 $\pm$ 101	141 $\pm$ 107	306 $\pm$ 74
Pa_{CO_2} (torr)	38 $\pm$ 5	40 $\pm$ 6	43 $\pm$ 11	43 $\pm$ 10	44 $\pm$ 12	43 $\pm$ 10
$P\bar{v}_{O_2}$ (torr)	54 $\pm$ 5	59 $\pm$ 15	53 $\pm$ 10	48 $\pm$ 10	48 $\pm$ 9	56 $\pm$ 6
$\dot{V}_{O_2}$ (ml/min/m²)	112 $\pm$ 27	100 $\pm$ 28	105 $\pm$ 16	107 $\pm$ 16	109 $\pm$ 20	105 $\pm$ 10
Cardiac index (L/min/m²)	2.75 $\pm$ 0.42	3.38 $\pm$ 0.84	3.49 $\pm$ 0.69	3.37 $\pm$ 0.89	3.25 $\pm$ 0.82	3.05 $\pm$ 0.69
PVR (torr·min·m⁻⁵)	2.71 $\pm$ 0.92	2.82 $\pm$ 1.33	3.31 $\pm$ 1.29	3.24 $\pm$ 1.22	3.56 $\pm$ 2.87	3.20 $\pm$ 1.56
Heart rate (beats/min)	78 $\pm$ 10	88 $\pm$ 14	90 $\pm$ 14	92 $\pm$ 14	87 $\pm$ 18	81 $\pm$ 17

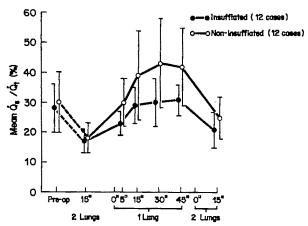* Values are means $\pm$ SD. Abbreviations are defined in footnote to Table 1.

FIG 1. Plot of mean (±SD) intrapulmonary shunt against time for insufflated and non-insufflated patients. Preoperative data plotted merely to illustrate similarity of both groups in prestudy period. Statistically significant differences ($p < 0.05$) between two groups of patients during one-lung ventilation occurred at 15, 30, and 45 minutes.
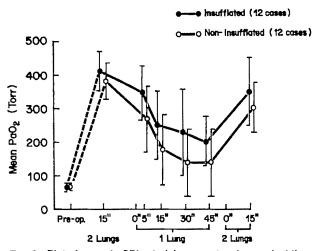

FIG 2. Plot of mean (±SD) arterial oxygen tension against time for insufflated and non-insufflated patients. Preoperative data plotted merely to illustrate similarity of both groups in prestudy period. Statistically significant group differences ($p < 0.05$) occurred during period of one-lung ventilation.

peated measures analysis of variance technique showed a statistically significant interaction between the two groups ($p < 0.01$). This implies that the two groups behaved differently over time. For this reason the data were subjected to the Newman-Keuls multiple comparisons analysis, which showed a significant difference between groups at 15, 30, and 45 minutes into the period of OLV ($p < 0.05$). At these times the patients in group 1 (insufflated) had a significantly lower shunt fraction than those in group 2 (non-insufflated).

None of the other factors subjected to repeated analysis of variance showed significant interaction.
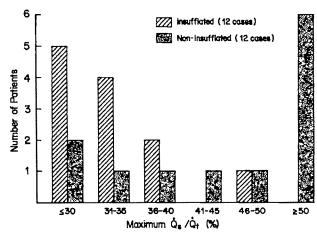
FIG 3. Distribution of maximum measured intrapulmonary shunt for each patient during one-lung ventilation. Comparison of distribution for insufflated and non-insufflated patients is shown.
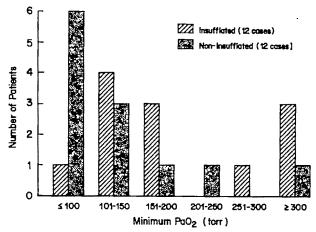
FIG 4. Distribution of minimum measured arterial oxygen tension for each patient during one-lung ventilation. Comparison of distribution for insufflated and non-insufflated patients is shown.

However, Pa_{O_2} was the only variable without interaction that exhibited a significant difference between groups ($p < 0.05$). No interaction indicates that both groups responded in similar fashion over time. The statistically significant group effect indicated that the Pa_{O_2} in group 1 (insufflated) was consistently different (higher) from that in group 2 (non-insufflated) over time.

Pa_{CO_2}, $\dot{V}_{O_2}$, and PVR were the only variables analyzed that showed no significant time effect. All other variables showed a statistically significant time effect ($p < 0.05$). Cardiac index, oxygen delivery, heart rate, MPAP, and PAWP showed a significant increase with time on OLV. MAP, LVSWI, and SVR all decreased significantly with time. $P\bar{v}_{O_2}$ was the only variable that exhibited an initial increase and a subsequent decrease with time during OLV. Although these varia-

bles had time effects, none had significant group effects.

Discussion

The results of this study show that: (a) there was a significant increase in $\dot{Q}_s/\dot{Q}_t$ and decrease in Pa_{O_2} with and without oxygen insufflation as a function of time during OLV, (b) peak increases in $\dot{Q}_s/\dot{Q}_t$ occurred after 30 minutes of OLV in the patients that were not insufflated and at 45 minutes in the patients who received oxygen insufflation, (c) the increase in $\dot{Q}_s/\dot{Q}_t$ was significantly greater in patients who did not receive oxygen insufflation during OLV, and (d) Pa_{O_2} showed a significant group effect and was consistently lower in patients not given oxygen by insufflation than in patients in whom oxygen was insufflated.

No previous study has evaluated the effects on Pa_{O_2} and $\dot{Q}_s/\dot{Q}_t$ of continuous insufflation of oxygen to the nonventilated lung under clinical conditions during OLV. O'Shea et al (5), using patients as their own controls, demonstrated that hypoxemia can be reversed by intermittent inflation of the nonventilated lung with oxygen. Capan et al (8), by insufflating oxygen with PEEP of 10 cm H_2O into the nonventilated lung, also improved arterial oxygen tension levels during OLV. Both O'Shea and Capan and their co-workers attempted to determine the effects of oxygen insufflation to the nonventilated lung; O'Shea et al concluded that oxygen insufflation under positive pressure to the nonventilated lung did not improve Pa_{O_2} levels after 10 minutes of deflation. All patients in their study also received PEEP of 4 cm H_2O to the ventilated lung throughout. Capan et al concluded that oxygen insufflation to the nonventilated lung without positive pressure did not improve $\dot{Q}_s/\dot{Q}_t$ or Pa_{O_2} levels whether PEEP was applied to the ventilated lung or not. These discrepancies may be the result of previous manipulations and the extended time of OLV due to the fact that patients were used as their own controls. Surgical manipulation was also discontinued 5 to 10 minutes before sampling, thus introducing into the experimental design an additional variable from the usual clinical situation.

The present study was designed to evaluate the effects on $\dot{Q}_s/\dot{Q}_t$ and Pa_{O_2} of continuous oxygen insufflation to the nonventilated lung during OLV in two similar groups of patients in clinical situations. The observed beneficial effect on $\dot{Q}_s/\dot{Q}_t$ and Pa_{O_2} levels of continuous oxygen insufflation to the nonventilated lung during OLV could be due to the fact that significant numbers of alveolar capillary units in the nonventilated lung contribute to the shunt fraction and that these capillary units are in continuity with the proximal airway and thus benefit from oxygen insufflation.

All lobectomies in this study were performed in the lateral decubitus position, and during OLV the operative lung was allowed to collapse. Ventilation of the dependent lung only can lead to arterial oxygen desaturation even with the use of high concentrations of inspired oxygen (9). If significant perfusion to the nonventilated lung persists, arterial desaturation would occur due to ventilation perfusion ($\dot{V}/\dot{Q}$) mismatch or right-to-left intrapulmonary shunting (10). Several factors are important in decreasing perfusion to the nonventilated lung. Hydrostatic pressure relationships in the pulmonary artery in the lateral decubitus position tend to cause preferential perfusion of the dependent lung (11). Hypoxic pulmonary vasoconstriction (HPV) tends to redistribute blood to lung regions with higher alveolar oxygen tensions (12, 13). As the nonventilated lung collapses, the radii of vascular structures decrease, leading to increased PVR and redistribution of blood flow to ventilated areas of lung (10). As the nonventilated lung collapses, atelectasis resulting in right-to-left intrapulmonary shunting due to gravitational effects has also been reported (14, 15). Volatile anesthetic agents block HPV in man (13) although reports on their ability to block HPV in animal studies are conflicting (12, 16).

Randomization of patients and standardization of procedures according to a protocol were used to minimize inadvertent differences between the two groups that might have introduced bias into the results. Similarity of preoperative data in both groups of patients cannot explain the statistical differences observed in the two groups.

During the study Pa_{CO_2}, $\dot{V}_{O_2}$, and PVR did not change significantly between the two groups of patients nor did they change significantly with time. Elevation in the MPAP can result in redistribution of blood flow from the ventilated to the nonventilated lung by decreasing the beneficial effects of the hydrostatic presure in the pulmonary artery (11). No significant difference in the MPAP between the two groups was detected. Decreased cardiac output in the presence of $\dot{V}/\dot{Q}$ mismatch or absolute shunt results in an additional decrease in Pa_{O_2} (17). Again, no significant difference in cardiac index was demonstrated between the two groups during the procedure. No other index likely to affect the degree of $\dot{Q}_s/\dot{Q}_t$ differed significantly between the two groups of patients. The observed increase in cardiac index, heart rate, MPAP,

PAWP, and oxygen delivery, together with the decrease in $P\bar{v}_{O_2}$, MAP, LVSWI, and SVR with time is a function of the physiologic response to this anesthetic and surgical procedure and did not differ significantly between the two groups.

Therefore, it seems probable that even during collapse of the lung, some alveolar capillary units remain in continuity with the proximal airways, facilitating gas exchange during oxygen insufflation and reducing intrapulmonary shunting during OLV.

In conclusion, continuous insufflation of oxygen to the nonventilated lung during one-lung ventilation, in the absence of PEEP to either lung, effectively minimized the degree of intrapulmonary shunting and attenuated the decrease in arterial oxygen tension over the first 45 minutes of one-lung ventilation in the vast majority of patients. This simple and inexpensive technique can be applied to patients undergoing one-lung ventilation with beneficial results.

ACKNOWLEDGMENTS

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Continuous Monitoring of Mixed Venous Oxygen Saturation in Critically Ill Patients

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BAELE, P. L., McMICHAN, J. C., MARSH, H. M., SILL, J. C., AND SOUTHORN, P. A.: Continuous monitoring of mixed venous oxygen saturation in critically ill patients. Anesth Analg 1982;61:513-7.

A new pulmonary artery balloon flow-directed catheter combines a fiberoptic photometric system for continuous display of mixed venous blood oxygen saturation ($S\bar{v}_{O_2}$) with the capacity for hemodynamic measurements including thermodilution cardiac output estimation. This oximetry system was studied to determine its accuracy, reliability, and usefulness in the surgical intensive care unit (ICU). Twenty-two catheters were tested, but only 17 were successfully placed in 16 patients. There were technical problems associated with 10 catheters and on six occasions these necessitated the use of another catheter. The catheter values for $S\bar{v}_{O_2}$ were closely related ($r = 0.9516$) to those obtained from a laboratory Co-oximeter. Continuous monitoring of $S\bar{v}_{O_2}$ is accurate and valuable as a warning system for deterioration in cardiopulmonary function and as an indicator of the effects of various therapeutic maneuvers in critically ill patients.

Key Words: MEASUREMENT TECHNIQUES: venous oxygen; OXYGEN: mixed venous.

PREVIOUS studies have described in vivo continuous monitoring of mixed venous blood oxygen saturation ($S\bar{v}_{O_2}$) by fiberoptic reflectometry. The method was introduced as a promising tool in various clinical situations including diagnostic cardiac catheterization (1, 2) and intraoperative and postoperative monitoring in cardiac surgery (3, 4). Technical problems have, however, delayed clinical investigation and the widespread use of the technique. Technical problems included catheter stiffness, lack of thermodilution cardiac output determination capability, difficult standardization, need for frequent recalibration, and fibrin deposits occluding the tip of the catheters.

A new fiberoptic reflectometry system (Oximetrix, Mt. View, CA), connected to a thin umbilical catheter, has been described and evaluated in neonates (5). The instrument was found to be accurate, easy to standardize, and reliable over long periods of time. Its rapid response time allowed its use as a guide for oxygen therapy and assisted ventilation. This system has now been coupled to a new pulmonary arterial flow-directed catheter (Oximetrix Opticath), combining the fiberoptic reflectometric system for continuous display of $S\bar{v}_{O_2}$ with the capacity for hemodynamic measurements including thermodilution cardiac output estimation. This paper presents our initial evaluation of the accuracy of this device and its usefulness in the clinical care of critically ill patients.

Methods and Materials

The system for reflection spectrophotometry has been described in detail elsewhere (5). In brief, light-emitting diodes generate alternating pulses of three different wavelengths (between 600 and 1000 nm), 244 times per second. The light is transmitted to the tip of the catheter through a fiberoptic channel and is absorbed, refracted, and reflected by the red blood cells. A second fiberoptic channel conducts the reflected light to a photodetector. Blood reflectance changes with variations in its colored constituents, e.g., hemoglobin, oxyhemoglobin, carboxyhemoglobin, sulfhemoglobin, and methemoglobin. The oxygen saturation of hemoglobin is derived by a computer from the relative intensities corresponding to the three different wavelengths. A digital readout shows the average value for the preceding 5 seconds

and is updated every second. A two-speed paper recorder allows further analysis of changes in saturation. Audible and visible alarms warn when light intensity varies. This may happen when the tip of the catheter faces a vessel wall, is in the wedge position, is covered with fibrin deposit, or when the fiberoptics are damaged.

The catheter is #7½ French in size and is constructed from polyvinylchloride. It contains a distal (pulmonary arterial) and a proximal (right atrial) lumen for pressure monitoring, blood sampling, or fluid injection. A thermistor is located approximately 3 cm from the tip and a 2-ml inflatable balloon is at the extremity. Two fiberoptic channels provide in vivo reflectometry. The catheter is calibrated either before insertion by using a reference surface supplied with the catheter, or after insertion by adjustment to $S\bar{v}_{O_2}$ determinations made by a reliable Co-oximeter on pulmonary arterial blood samples.

Twenty-two catheters were tested. Five were excluded from the study because of problems occurring at the time of insertion. These are indicated by "0" in the Table; therefore, 17 catheters were evaluated. These 17 catheters were placed in 16 critically ill adults who required hemodynamic monitoring. At the time of the study, 13 patients were in acute respiratory failure from a wide variety of causes and all required mechanical ventilation with oxygen-enriched air.

Using an aseptic technique, each of 17 catheters was inserted via a #8 French introducer (Cordis) into a central vein (6) via either the internal jugular or subclavian approach. The correct position of the catheter in the pulmonary artery was assessed by pressure wave form monitoring and confirmed by roentgenography. Seven catheters were calibrated before insertion, the others after insertion. If the system had to be disconnected from its power source, recalibration was performed during use.

A continuous infusion of heparinized 5% dextrose in water (4 ml/hr) was used to prevent occlusion of the catheter lumina. The pulmonary arterial pressure wave form was continuously displayed until removal of the catheters. Samples of pulmonary arterial blood (2 ml) were withdrawn slowly through the distal lumen on 124 occasions and analyzed in vitro for $S\bar{v}_{O_2}$ using a four-wavelength photometric method (IL 282 Co-oximeter). This instrument was calibrated daily with commercially available reference solutions. The laboratory values (in vitro values) of $S\bar{v}_{O_2}$ were compared, by linear regression analysis, with coincident readings of the fiberoptic system (in vivo values). In vivo and in vitro values of $S\bar{v}_{O_2}$ were also obtained at the time of cardiac output estimations.

This work was performed in accordance with the ethical standards of the Human Studies Committee of the Mayo Clinic.

Results

Accuracy of Fiberoptic Oximeter System

The regression analysis of the 124 paired in vivo and in vitro $S\bar{v}_{O_2}$ measurements (Fig 1) shows a good correlation ($r = 0.9516$, $Sy \cdot x = 3.562$).

The Student's paired t-test disclosed that the differences observed between results obtained with the two methods were not statistically different from zero ($p = 0.472$).

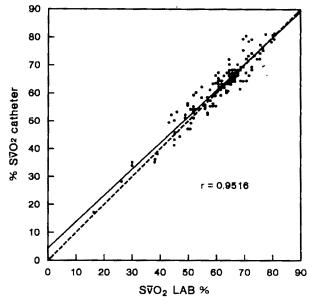The catheters were left in place for an average of

TABLE

Technical Problems with Catheters*

	Incidence	Time after Insertion
		hr
Hold-up in right ventricle	3	0†, 0†, 0†
Balloon rupture	3	0†, 26, 44†
Thermistor failure	1	1†
Broken fiberoptics	2	0, 52
Occluded lumen	1	56
Total	10	

* Zero indicates during insertion.
† Problem necessitated use of another catheter.

Fig 1. Mixed venous oxygen saturation ($S\bar{v}_{O_2}$) as calculated in the laboratory (LAB) plotted against value obtained from oximetry system (catheter). r = correlation coefficient.

40 hours (range: 1 hour 20 minutes to 102 hours). With the exception of accidental damage to the fiber-optics (two catheters) or disconnection, the system functioned well until the end of the study in every case. Damage to the fiberoptics did not prevent use of the catheter for hemodynamic monitoring and cardiac output estimation.

The system was not recalibrated once in place and functioning. The difference between in vivo and in vitro measurements was within ±4% or 82% of paired values and $S\bar{v}_{O_2}$ increased by 0.6% of saturation for each 24 hours the catheters were in place (Fig 2). As the manufacturer suggests recalibration once a day, the observed drift should be considered clinically insignificant.

The following factors were shown by multivariate analysis not to affect the accuracy of the system: method of calibration, hemoglobin concentration, body temperature, and cardiac index.

Technical Performance of Catheters and Complications

Twenty-two catheters were tested. Problems that arose with 10 catheters are presented in the Table. As previously mentioned, five problems occurred at the time of insertion and prevented further study of those particular catheters. Three of these could not be passed from the right ventricle into the pulmonary artery. The use of fluoroscopy disclosed that these catheters tended to lodge in the apex of the ventricle. In one instance the balloon had to be deflated in order to pass from the right ventricle to the pulmonary artery. Among the remaining 17 catheters, five additional problems were encountered (Table).

Premature ventricular contractions or short episodes of ventricular tachycardia (three patients) were associated with the placement of 14 catheters. Eight patients required lidocaine during passage of the catheter through the right ventricle. One patient, with severe chest trauma, successively developed a right

bundle branch block, ventricular tachycardia, and sinus bradycardia.

Clinical Applications

Continuous measurement of $S\bar{v}_{O_2}$ provided assessment of the efficacy of many therapeutic maneuvers as well as a means of detecting changes in oxygen delivery deserving of urgent clinical response. Examples follow.

Routine nursing procedures such as patient turning and patient bathing frequently result in rapid and large decreases in $S\bar{v}_{O_2}$ (Fig 3). The mechanism for this can be partly explained by increased peripheral utilization of oxygen associated with muscular activity and also altered ventilation-perfusion matching in the lung.

In a patient with acute respiratory failure requiring mechanical ventilatory support and positive end-expiratory pressure, discontinuance of this support for a short period resulted in a decrease in the value of $S\bar{v}_{O_2}$ from 58% to 32%. After the previous mechanical ventilatory support was resumed, 10 minutes elapsed before the original value of $S\bar{v}_{O_2}$ was obtained (Fig 4).

On the assumption that respiratory gas exchange and peripheral oxygen utilization remain constant, $S\bar{v}_{O_2}$ can be a valuable indicator of cardiac function. In a patient who was hypovolemic following surgery, alterations in cardiac output can be inferred from and demonstrated by changes in $S\bar{v}_{O_2}$ following the administration of intravenous fluids (Fig 5).

The use of the oximetry system as a warning device for impending severe cardiopulmonary failure has been documented. In this example (Fig 6), $S\bar{v}_{O_2}$ de-

FIG 2. Percentage difference between in vivo and in vitro $S\bar{v}_{O_2}$ as function of duration of catheter in pulmonary artery.

drift = 0.674% $S\bar{v}O_2$ per 24 hours

Time since calibration (hours)
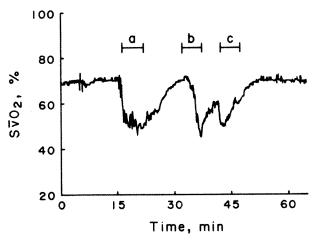
FIG 3. Effect on $S\bar{v}_{O_2}$ of suctioning tracheal tube (a), bathing and weighing (b), and turning patient and changing bed linen (c). Note prolonged duration of $S\bar{v}_{O_2} < 60\%$.
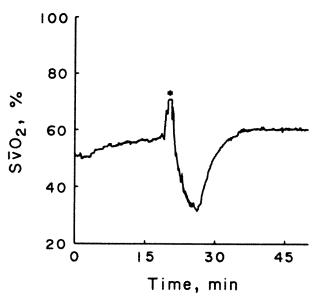
FIG 4. Cessation of mechanical ventilation during measurement of pulmonary wedge pressure produced immediate decrease in $S\bar{v}_{O_2}$. * indicates catheter balloon inflated.
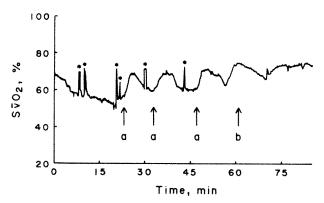

FIG 5. Effect of successive 100-ml intravenous boluses of lactated Ringer's solution (arrow "a") to reverse downward trend in $S\bar{v}_{O_2}$ and subsequent maintenance of normal $S\bar{v}_{O_2}$ by increased rate of infusion of same solution (arrow "b"). * indicates catheter balloon inflated to measure pulmonary wedge pressure.

creased rapidly over a period of 20 minutes before cardiac arrest occurred.

Discussion

Accuracy of Catheters

Two previous evaluations of this fiberoptic oximeter have been reported, the first using a thin umbilical catheter to monitor aortic blood saturation in neonates (5) and the other using a pulmonary arterial flow-directed thermodilution catheter during and after cardiac surgery (7). In these studies oxygen saturation was rarely less than 60%.
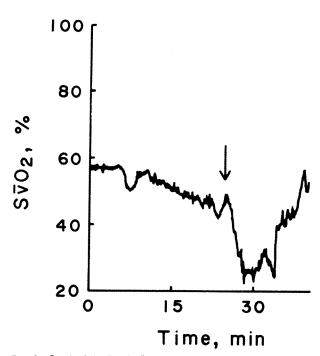
FIG 6. Gradual decline in $S\bar{v}_{O_2}$ over 20 minutes heralded onset of cardiac arrest (arrow) for which resuscitation was successful.

The current study was performed in an intensive care setting in a group of critically ill patients. It demonstrates the accuracy of this device over a wide range of values of $S\bar{v}_{O_2}$ (Fig 1). In the conditions encountered during the study, hemoglobin concentration, body temperature, and cardiac output did not affect the accuracy of the system, which showed a drift of less than 1% of saturation per day. Daily recalibration should diminish this source of error.

Both catheter design and inexperience with this particular type of pulmonary arterial catheter may have contributed to the high incidence of catheter failures. A second generation of catheters has been produced since this study was performed and, in our experience, the incidence of technical problems has now lessened with these new catheters. However, the catheters are still relatively stiff and this may be partly responsible for difficulties encountered in passing the catheter into the pulmonary artery and for some of the failures occurring after placement. In the light of our experience, we suggest special care in the handling of the catheter balloon, consideration of the right jugular route for its insertion, and availability of fluoroscopy during placement.

Clinical Applications

The degree of hemoglobin oxygen saturation in mixed venous blood is an indicator of oxygen transfer

across the alveolar capillary membrane in the lung, of cardiac output, and of peripheral tissue utilization of oxygen. Oxyhemoglobin saturation also depends on the shape of the oxyhemoglobin dissociation curve which reflects the hemoglobin affinity for oxygen, the latter varying with pH; arterial carbon dioxide tension; temperature; and the level of 2,3-diphosphoglyceric acid in erythrocytes. Mixed venous oxygen saturation thus reflects pulmonary and cardiac function, tissue blood flow, and oxygen consumption. A decrease in $S\bar{v}_{O_2}$ can be due to decreased oxygen transfer at the lung, decreased oxygen transport to the tissues, or increased tissue utilization of oxygen. An increasing $S\bar{v}_{O_2}$ indicates improvement in pulmonary oxygen uptake or cardiac output or decreased peripheral oxygen utilization such as that associated with a decrease in body temperature, cyanide poisoning (8), and sepsis.

The relationship between mixed venous oxygen saturation or content and cardiopulmonary function can be demonstrated by rearranging the Fick equation as follows:

$$C\bar{v}_{O_2} = Ca_{O_2} - \frac{\dot{V}_{O_2}}{CO}$$

where $C\bar{v}_{O_2}$ and Ca_{O_2} are the mixed venous and arterial contents of oxygen, $\dot{V}_{O_2}$ is oxygen consumption, and CO is cardiac output. Appreciation of this relationship provides a basis for understanding changes observed by continuous monitoring of $C\bar{v}_{O_2}$. The factors in this equation are interdependent. Changes in one may produce compensatory changes in another without an alteration in $C\bar{v}_{O_2}$. For example, a decrease in Ca_{O_2} may be fully compensated for by an increase in CO.

The Oximetrix oximetry system provides the means for continuous monitoring of both $S\bar{v}_{O_2}$ and CO. These data, combined with an arterial blood gas analysis, provide detailed information regarding oxygen delivery to and extraction by the tissues. The system can thus be used both as a monitor of therapeutic maneuvers and as an alarm device for important changes in cardiopulmonary function. A value of $S\bar{v}_{O_2}$ less than 60% in the presence of adequate respiratory gas exchange indicates inadequate cardiac

function (4) or high tissue oxygen consumption. It is now our practice to ask the nursing staff to inform the doctor immediately if the value of $S\bar{v}_{O_2}$ decreases to less than 60% and it is at this level that we routinely set the lower limit alarm on the computer.

In conclusion, our initial studies of the reflectance oximetry system show that continuous monitoring of mixed venous blood oxygen saturation is feasible and accurate over a wide range of mixed venous oxyhemoglobin saturation values. Although technical problems were frequently encountered with the original design of the catheters, we nevertheless found the system to be a valuable indicator of the effects of therapeutic maneuvers on cardiopulmonary function and a useful warning system for deterioration in these functions. These features, combined with its rapid response time, characterize a monitoring system that will be of value for the care of the critically ill patient.

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Painful Trigger Points in Surgical Scars

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DEFALQUE, R. J.: Painful trigger points in surgical scars. Anesth Analg 1982;61:518–20.

A group of 69 patients with painful trigger points in operative scars were treated following abdominal, inguinal, lumbar, or extremity surgery. Patients undergoing thoracotomies, neurosurgical procedures, or limb amputations, and patients with neurotic features or seeking secondary gains were excluded. The diagnosis was made by finding one or more definite, consistent, tender trigger points in the scar in which total, transient relief of pain was provided by injection of bupivacaine. Repeated injections of alcohol into the trigger point proved to be a simple, safe, and effective treatment with permanent cure or marked improvement in 63 (91%) patients.

Key Words: PAIN: trigger points; ALCOHOL: injection.

PAINFUL surgical scars remain a subject of confusion in the medical literature (1–5). One cause of painful scars, we believe, is the presence in the incision of one or more definite, exquisitely tender, trigger points, probably small scar-entrapped neuromas of terminal branches of a sensory nerve. We present our clinical findings and treatment of this syndrome in 69 patients.

Clinical Material

From a group of patients with painful postoperative scar seen between 1969 and 1978 we chose 69 patients who met the following conditions: (a) Palpation of the scar elicited one or more painful trigger points. Two injections of those points with bupivacaine produced complete, although transient, pain relief. (b) The scar resulted from surgery in the inguinal (32 cases), abdominal (14 cases), or lumbar (16 cases) areas or in an extremity (two arms, five legs). Patients undergoing thoracotomies, operations on peripheral nerves, or limb amputations were excluded. (c) Patients no longer working or seeking compensation, and those with neurotic features were also excluded. The reasons for this rigid selection are presented in the discussion.

There were 45 male and 24 female patients between the ages of 23 and 48 (average 36) years. Each patient had consulted at least two physicians (maximum seven) over a period of 7 months to 4 years. Forty-

seven patients had been told that their pain was functional, seven had been referred to a psychiatrist, and nine to a pain clinic.

Symptoms

The symptoms of the 69 patients were remarkably similar and consistent. (a) The pain appeared 1 to 5 (average 2) weeks after surgery. It rapidly reached its maximal intensity and remained unchanged. It did not respond to local applications of heat or cold. Non-narcotic analgesics gave insufficient relief. (b) The pain was a severe, gnawing ache, often with a burning component. Skin hyperesthesia was common. The discomfort was constant but was aggravated by postures or movements that tensed the muscles or fasciae incised at surgery, e.g., deep breaths, changes in posture, defecation, intercourse, twisting of the trunk, reaching for highly placed objects, etc. The patients quickly learned to avoid most of these movements. In 13 (19%) patients those motions not only aggravated the pain but also produced paresthesiae along the dermatome of the incision. (c) Thirty-four (49%) patients consistently pointed to a specific place in their scar as the source of their pain; the 35 (51%) others were less accurate or consistent in locating their pain. (d) Systematic, deep palpation of the scar with the blunt tip of a pencil elicited at least one sharply localized, consistent trigger point. Pressure on that point reproduced and aggravated the spontaneous pain, and in 48 (69%) patients it caused anterograde and/or retrograde paresthesiae in the sensory dermatome of the incision. All but three patients had a single trigger point. Two patients had two trigger

points and a third patient had three trigger points in her vertical cholecystectomy incision. (e) Sixty-one (88%) patients had a least one unsightly area in their scar, often the result of a small wound infection. In 57 patients the trigger point was situated in that area; in four others the painful scar resulted from a stab wound made to insert a drain.

Diagnosis

The trigger point was precisely located by repeated palpation of the scar and marked with a skin pencil. A 25-gauge, 4-cm long or a 22-gauge, 6-cm long needle was inserted perpendicular to the skin at that mark and slowly advanced with small, fanwise thrusts until its tip was felt to enter a hard nodule of scar tissue and simultaneously caused sharp pain and paresthesiae. This occurred at a depth of 1.5 to 4.5 cm. Each patient located that trigger point without hesitation. Then 1 to 3 ml of bupivacaine 0.75% with epinephrine 1:200,000 was injected in the nodule, reproducing pain and paresthesiae. An injection was given in each point of the three patients with multiple trigger points. The patients, unaware of the duration of action of the injected bupivacaine, were asked to time the recurrence of their pain. In all patients one block produced complete pain relief and a small area of anesthesia lasting for 6 to 10 hours. A second bupivacaine block was repeated a few days later with similar results.

Treatment

Absolute alcohol (1 ml) in a tuberculin syringe was injected over a 10-minute period in each trigger point after it had been located again with the 25- or 22-gauge needle (73 points, 69 patients). All patients complained of an excruciating, burning pain and of paresthesiae during and up to 5 minutes after the alcohol injection. Seventeen patients received small intravenous doses of fentanyl before and during the block. All remained supine and quiet for 30 minutes after the injection to prevent the diffusion of the alcohol and thus enhance its efficacy. Most alcohol blocks had to be repeated to produce permanent relief (see "Results"). An identical protocol was followed for the subsequent blocks.

Results

The results were ascertained by repeated interviews for at least 12 months after the last block. Six (9%) patients had no permanent improvement after six alcohol injections. Each block produced only a few

days of relief. No other treatment was recommended and the benign nature of their syndrome was emphasized to those patients. Sixty-three (91%) patients had improvement at the 12-month interview. (a) In 16 (23%) the severe pain and the paresthesiae were gone but some discomfort or ache persisted, especially with the movements or postures straining the incision. (b) In 47 (68%) patients the pain and the paresthesiae had completely disappeared.

Of the 63 improved or cured patients, six required one alcohol block, nine received two blocks, 38 had three blocks, and 10 needed four to six blocks. The first alcohol block generally lasted from a few days to a few weeks; subsequent blocks lasted from a few weeks to several months. Thirteen patients had a small area of numbness in and around the incision but did not find it uncomfortable. There were no other complications.

Discussion

The location of the trigger points in a hard nodule of scar, the neuralgia and paresthesiae reproducible by needling of that nodule, the distribution of the paresthesiae, and the total pain relief produced by small amounts of anesthetic or neurolytic agent suggest that the trigger points are scar-entrapped neuromas of small cutaneous branches of a sensory, or mainly sensory, nerve, viz: (a) the ilioinguinal or genitofemoral nerves in the inguinal area, (b) the anterior or lateral cutaneous branches of the lower (T8-12) intercostal nerves or of the iliohypogastric nerve following abdominal or lumbar incisions, and (c) the lateral antebrachial cutaneous or radial nerve in the forearm, and the saphenous or the posterior femoral cutaneous nerve in the leg.

The depth of the trigger points and the texture of the surrounding tissue as revealed by needle probing suggest that those neuromas lay in, or just outside, a myofascial plane, e.g., the posterior rectus sheath or the transverse muscle or its aponeurosis in the trunk, and the superficial fasciae in the extremities. Such small neuromas have been mentioned elsewhere (1–3, 5) as a cause of postoperative scar pain.

We emphasize that alcohol blocks are not a panacea for every incisional pain and that they only provided safe and successful treatment in the small, scar-entrapped neuromas described here. Painful scars have various other causes. Some scars, for instance, are excruciatingly painful, tender, and dysesthetic over their entire length without any detectable trigger point. The cause of this syndrome remains unknown and its treatment frustating (1, 2). Large nerves may

be damaged during an operation or become entrapped by surgical scar, as in the ilioinguinal, genitofemoral, or femoral neuropathies seen after a herniorrhaphy (6). Painful neuromas also occur after surgical sectioning of any large nerve (6). The mechanism of the intercostal neuralgias seen after thoracotomy remains undefined; central factors have been suggested to explain their intractability (6). And, finally, limb amputations often produce large and very painful neuromas. Their etiology, too, is complex and probably often involves central factors (6). Because those neuropathies have an intricate etiology and because they involve large, mixed nerves for which alcohol blocks are ill-advised (motor loss, anesthesia dolorosa, alcohol neuritis), they must be carefully distinguished from the small neuromas described here. Patients whose surgery may have led to those neuropathies as a cause of painful scar were excluded from our group (thoractomies, limb amputations, peripheral neurosurgery).

We also stress that no more than 1 ml of alcohol was injected and that all the trigger points were at least 1.5 cm under the skin. Superficial injection of large volumes of neurolytics inevitably leads to skin necrosis.

Our treatment has two drawbacks. First is the severe pain produced by the injection of alcohol in a patient who must remain alert to help locate the trigger point; this, however, can be alleviated by reassurances that the pain is brief and by the generous use of intravenous fentanyl. Second is the need to repeat the block in most patients, a fact noted elsewhere (5). Lest they become discouraged, both the patient and the physician must accept the possibility of the need for repeated injections of alcohol at the outset of the treatment.

Excluding patients with neurotic features or those seeking secondary gains certainly increased our success rate. However, we initially wanted to evaluate our treatment in highly favorable conditions. This restriction must be kept in mind when reviewing our results or when treating other patients.

Other treatments for painful, small incisional neuromas have been tried, including systemically administered drugs, physiotherapy transcutaneous electrical nerve stimulation (TENS), and repeated blocks with local anesthetic solutions, but the results have been disappointing (1–5). We feel that alcohol blocks, despite our reluctance to use them for a benign condition, are justified because of their simplicity, safety, and high rate of success.

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Comparison of Hemodynamic and Hormonal Effects of Large Single-Dose Fentanyl Anesthesia and Halothane/Nitrous Oxide Anesthesia for Coronary Artery Surgery

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ZURICK, A. M., URZUA, J., YARED, J.-P., AND ESTAFANOUS, F. G.: Comparison of hemodynamic and hormonal effects of large single-dose fentanyl anesthesia and halothane/nitrous oxide anesthesia for coronary artery surgery. Anesth Analg 1982;61:521–6.

This study was conducted to compare our standard halothane/N_2O anesthetic technique with large single-dose fentanyl (150 µg/kg)/O_2 anesthesia in patients undergoing coronary artery surgery. We chose to look at two discrete stimuli (tracheal intubation and sternotomy) and measured changes in mean arterial pressure, heart rate, mean pulmonary artery occluded pressure, PAO cardiac output, derived indices (stroke volume, rate-pressure product, systemic vascular resistance, and changes in the plasma concentrations of growth hormone, epinephrine, norepinephrine, and renin activity. Both groups of patients were comparable in age, height, weight, and surface area. Variance in hemodynamic functions did not reach undesirable levels in either group. In the patients given fentanyl, there was a significant increase in heart rate after pancuronium administration. Mean arterial pressure and mean pulmonary artery occluded pressure did not change significantly from control values in either group; however, there was enough divergence between groups for the changes to be statistically significant. Cardiac output decreased in both groups after sternotomy. There was no significant change in systemic vascular resistance in either group. The only significant hormonal change was a significant increase in plasma levels of growth hormone in patients who received halothane/N_2O for anesthesia ($p < 0.001$). Plasma fentanyl concentrations decreased rapidly after bolus administration consistent with pharmacokinetics previously described. Of the 10 patients given fentanyl two were aware during sternotomy; of the 12 patients in the halothane group none had awareness. We believe that large-dose fentanyl offered better preservation of coronary perfusion and more attenuation of the hormonal flux observed with stress than halothane/N_2O anesthesia. Large-dose fentanyl may offer more advantages in patients with greater ventricular impairment.

Key Words: ANALGESICS: fentanyl; ANESTHETICS, Volatile: halothane; ANESTHESIA: cardiovascular.

OPIATES have a long history of use in clinical anesthesia (1), but the administration of large

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doses of opiates as a primary anesthetic is relatively recent, especially for anesthesia in cardiac surgery (2). Large doses of morphine and fentanyl have become particularly popular for anesthesia for cardiac surgical procedures (3, 4). With the development of new synthetic opiates, there is urgent need for objective data documenting the hemodynamic and hormonal changes induced by anesthetic doses of narcotics (5). It has been reported that fentanyl when used in large doses (50 to 100 µg/kg) for induction of anesthesia is associated with little or no change in measured hemodynamic indices (1, 6). Large-dose fentanyl has also been associated with blunting of the normal hormonal responses associated with the stress of anesthesia and surgery (6). This has prompted some to

label large-dose fentanyl as a "stress-free" anesthetic. By comparing large-dose fentanyl with our standard halothane/nitrous oxide technique we sought to determine whether significant differences in hemodynamic stability or hormonal changes occurred in cardiac surgical patients given different types of anesthesia.

Methods

Institutional approval and written consent for additional blood sampling during the operation were obtained from all patients.

Twenty-two patients with symptomatic atherosclerotic coronary artery disease undergoing elective coronary revascularization operations were prospectively studied (Table 1). All patients were white men. Anesthesia for all was induced between 7:30 and 10:00 a.m. to minimize changes due to circadian variation in growth hormone levels. None had hypertension, diabetes, or any associated pathology. Ventricular function was angiographically classified as normal or mildly impaired. All patients were receiving therapy for angina; 17 received propranolol, 40 to 160 mg daily, including on the morning before surgery. All patients received morphine sulfate, 0.15 mg/kg, and scopolamine, 0.4 mg, intramuscularly for premedication. All patients also received nitroglycerin paste, 1½ inch, with the preoperative medications.

The patients were divided into two groups: Group 1 was comprised of 10 patients, each of whom received large-dose fentanyl (150 μg/kg) for anesthesia. Group 2 was comprised of 12 patients, each of whom received halothane/nitrous oxide anesthesia. We measured systolic blood pressure (SBP), mean arterial pressure (MAP), and diastolic blood pressure (DBP), pulmonary artery occluded pressure (PAO), central venous pressure (CVP), heart rate (HR), cardiac output (CO) by thermodilution, and collected blood samples for measurement of plasma levels of epinephrine, norepinephrine, growth hormone, renin activity, and fentanyl at the following times: (a) after all monitoring lines had been placed, immediately before induction of anesthesia; (b) 5 minutes following intubation of the trachea; and (c) 5 minutes following sternotomy.

RA was measured by the rate of generation of angiotensin I (7). Catecholamine levels were determined by radioenzymatic techniques (8). Growth hormone levels were determined by radioimmunoassay (9). Plasma fentanyl levels were determined by radioimmunoassay (10).

Patients in group 1 were anesthetized with 150 μg/ kg of fentanyl citrate as the sole anesthetic agent. The

522

TABLE 1
Characteristics of Patients*

	Group 1 (fentanyl)	Group 2 (halothane)
No. of patients	10	12
Age† (yr)	58.7 ± 2.1	56.2 ± 2.2
Height† (cm)	169.4 ± 2.3	171.0 ± 1.7
Weight† (kg)	78.1 ± 3.4	74.8 ± 3.2
Body surface† (m²)	1.89 ± 0.05	1.87 ± 0.04
No. of grafts	2.7 ± 0.21	3.1 ± 0.23

* Values are means ± SE.
† Differences between groups not significant ($p > 0.05$)

total fentanyl dose was infused via a peripheral intravenous line as rapidly as possible (150 to 250 ml within 5 minutes). This corresponds to an infusion rate of 1500 to 2000 μg of fentanyl per minute. The patients breathed 100% O_2 via an anesthesia face mask. Muscle relaxants were given as follows: (a) pancuronium bromide, 1.5 mg IV, before the start of the fentanyl infusion; (b) succinylcholine, 100 mg IV, when the patient failed to respond to verbal stimuli; and (c) followed by the remaining total dose of 0.1 to 0.15 mg/kg of pancuronium bromide, concurrent with the infusion of the rest of the fentanyl.

Muscle rigidity was prevented by this sequence. When all the fentanyl had been infused, tracheal intubation was performed.

Patients in group 2 received sodium thiopental, 125 to 250 mg IV, for induction of anesthesia. With loss of consciousness and loss of palpebral reflex the patients were ventilated using a face mask with 50% O_2 and 50% nitrous oxide. They also received pancuronium, 0.1 to 0.15 mg/kg. Halothane 4% to 5% was added depending on the hemodynamic responses. When the systolic blood pressure had decreased approximately 20% from control values, laryngoscopy was performed and the trachea intubated. Anesthesia was then maintained with halothane in a concentration of 0.5% to 2.0% in the inspired air depending on the hemodynamic response of the individual patient.

Seven patients in group 2 received 100 to 400 μg of nitroglycerin intravenously if systolic blood pressure increased 20% above control levels after intubation. Propranolol was given to five patients (two in group 1 and three in group 2) for increases in HR above 110 beats per minute.

The following values were calculated from the hemodynamic measurements: systemic vascular resistance (SVR), stroke volume (SV), and rate-pressure product (RPP).

The data were analyzed by means of the Student's

t-test, both paired and unpaired, and $p < 0.05$ was selected as the level of statistical significance (11).

Results

Patients in both groups were comparable as to age, weight, body surface area, and number of grafts (Table 1).

Measured and derived hemodynamic values for both groups of patients are presented in Table 2. Statistically significant changes from control values for each group are noted, as are statistically significant differences between the groups. Although all the hemodynamic values reported here suggest that these anesthetics did not produce severe hemodynamic changes, induction was associated with considerable deviations from the preinduction values in several patients in both groups. Therapeutic interventions were required for patients in both groups as noted above. Halothane anesthesia was characterized by a slightly less stable cardiovascular course. Wide fluc-

tuations in cardiovascular functions could be observed between the times when measurements were made. This was not the case with patients who received fentanyl/O_2 anesthesia.

In Table 3 are presented the plasma levels of epinephrine, norepinephrine, renin activity, growth hormone, and fentanyl observed in both groups of patients. Statistically significant changes within a given group are noted, as are statistically significant differences between groups. In the Figure is shown that although plasma levels of growth hormone did not change from control levels in patients given fentanyl, they increased significantly in those receiving halothane ($p < 0.001$).

Discussion

This study evaluated two different anesthetic techniques in a highly selected group of white male patients with coronary artery disease, with normal or mild ventricular impairment, without any other med-

TABLE 2

Comparison of Hemodynamic Changes Produced by Fentanyl (Group 1) and Halothane (Group 2)*

Parameter	Group	Before induction	After intubation	After sternotomy
HR (beats/min)	1	66 ± 5.0	83 ± 4.7†	80 ± 3.3†
	2	67 ± 5.0	80 ± 4.8	69 ± 4.6
SBP (torr)	1	141 ± 10	133 ± 7.3	132 ± 6.7
	2	132 ± 7.2	110 ± 3.7†‡	109 ± 5.2†‡
MAP (torr)	1	98 ± 4.5	100 ± 5.2	97 ± 3.7
	2	89 ± 5.6	84 ± 3.9‡	83 ± 3.5‡
DBP (torr)	1	73 ± 4.5	80 ± 5.3	80 ± 3.3
	2	71 ± 4.7	70 ± 3.8	69 ± 2.7‡
PAO (torr)	1	11 ± 1.8	12.0 ± 1.4	11 ± 1.2
	2	13 ± 1.1	14.0 ± 1.7	16 ± 1.5‡
CVP (torr)	1	8.00 ± 1.88	10.4 ± 1.20	10.10 ± 1.59
	2	8.92 ± 1.10	10.5 ± 1.04	11.83 ± 1.60
CO (L/min)	1	5.6 ± 0.45	5.3 ± 0.73	4.4 ± 0.34†
	2	4.4 ± 0.41	4.4 ± 0.21	3.6 ± 0.17†
CI (L/min/m²)	1	2.93 ± 0.224	2.73 ± 0.322	2.29 ± 0.155†
	2	2.35 ± 0.213	2.37 ± 0.120	1.92 ± 0.107†
SVR (dyne · sec · cm⁻⁵)	1	1387 ± 157	1525 ± 144	1725 ± 170
	2	1491 ± 91	1349 ± 67	1623 ± 98
SV (ml/beat)	1	85.6 ± 4.8	63.4 ± 7.1†	55.0 ± 4.2§
	2	66.7 ± 4.7	56.6 ± 3.5	53.4 ± 4.3†
RPP (torr beats/min)	1	9246 ± 1076	11,000 ± 862	10,516 ± 588
	2	9110 ± 1107	8,169 ± 944‡	6,866 ± 799‡

* Values are means ± SE. Abbreviations used are: HR, heart rate; SBP, systolic blood pressure; MAP, mean arterial pressure; DBP, diastolic blood pressure; PAO, mean pulmonary artery occluded pressure; CVP, central venous pressure; CO, cardiac output; CI, cardiac index; SVR, systemic vascular resistance; SV, stroke volume; RPP, rate-pressure product.
† Difference from control values ($p < 0.05$).
‡ Difference between groups ($p < 0.05$).
§ Difference from control values ($p < 0.001$).

TABLE 3

Comparison of Changes in Blood Levels of Hormones in Patients who Received Fentanyl (Group 1) and Halothane (Group 2)*

	Group	Before induction	After intubation	After sternotomy
Epinephrine (pg/ml)	1	446 ± 264	88 ± 21	165 ± 56
	2	174 ± 54	64 ± 13	151 ± 28
Norepinephrine (pg/ml)	1	369 ± 39	499 ± 80	464 ± 93
	2	370 ± 58	395 ± 68	433 ± 102
Plasma renin activity (ng/ml)	1	2.3 ± 0.73	3.0 ± 0.96	3.8 ± 1.14
	2	2.3 ± 0.73	4.5 ± 2.7	4.7 ± 2.10
Growth hormone (ng/ml)	1	6.8 ± 4.6	5.0 ± 2.9	2.1 ± 0.9
	2	9.0 ± 6.3	20.2 ± 6.3[†]	36.8 ± 16.7[‡]
Fentanyl (ng/ml)	1	0.44 ± 0.15	105.55 ± 4.81[§]	32.97 ± 6.32[§]

* Values are means ± SE. Changes in concentration of fentanyl for those receiving fentanyl are rated.
† Difference between groups ($p < 0.01$).
‡ Difference between groups ($p < 0.001$).
§ Difference from control values ($p < 0.05$).
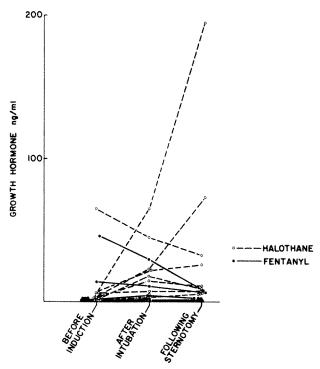
FIGURE. Differences observed in plasma levels of growth hormone as result of induction of anesthesia and surgery. Although constant during fentanyl anesthesia, increases were observed in most patients receiving halothane ($p < 0.001$).

ical problem, receiving only nitrates and beta-adrenergic blocking agents.

Hemodynamic Differences

Despite continuation of beta-adrenergic antagonists up to the time of surgery, HR increased in both groups after tracheal intubation. The increase was significant only in the patients given fentanyl. The increase in

HR occurred despite the large dose of fentanyl used. Increases in HR have been attributed to the use of pancuronium bromide, especially when given rapidly as a bolus, but an increase in HR has not been observed consistently by others who also used pancuronium for muscle relaxation in patients given fentanyl (1, 6, 12).

SBP, MAP, and DBP did not change significantly from control levels either after intubation or after sternotomy in patients given fentanyl. This is similar to the results reported by Sebel (1) for patients given 70 μg/kg of fentanyl. In a similar group of patients given 50 μg/kg of fentanyl, Waller et al (12) reported significant increases in SBP, MAP, and DBP. Sebel (1) reported a significant increase in DBP with sternotomy in patients given 60 μg/kg of fentanyl. It is possible that only a dose of fentanyl greater than 60 μg/kg is required to inhibit changes in arterial pressures associated with intubation and sternotomy.

Both MAP and DBP were significantly higher after sternotomy in the patients given fentanyl. $\overline{PAO}$ was significantly lower at the same time in patients given fentanyl. Taken together, the higher DBP and lower $\overline{PAO}$ reflect better coronary perfusion, which would be beneficial in patients with severe distal coronary artery disease where autoregulation may be lost and minimal coronary reserve is present (13-15).

The significant decrease in CO following sternotomy in both groups appears to be due more to mechanical factors, e.g., opening the chest (16, 17), than to actions of the anesthetics.

It is interesting to note that, although CO did not change significantly after intubation in either group, SV did decrease significantly after intubation in patients given fentanyl. A decrease in SV in patients

given fentanyl was also observed by Waller et al (12). The reduction of SV after intubation in patients given fentanyl in our study reflects the significant increase in HR that occurred at this time and does not represent an action of fentanyl per se. However, in this study SV was reduced to a comparable degree after sternotomy in both groups of patients. The decrease in SV after sternotomy in both groups reflects the mechanical events associated with this period (i.e., positive pressure ventilation, opening of the chest) rather than the action of the anesthetics.

The RPP was significantly higher after intubation and sternotomy in the patients given fentanyl than in patients given halothane. Although significantly greater than the RPP in patients given halothane, it was still within the normal range. However, it does indicate the possibility for increased O_2 consumption in patients given fentanyl for anesthesia.

Hormonal Differences

The adverse effects of the stress of anesthesia and surgery have been reviewed by Savage (18) and include both hypertension and tachycardia, neither of which is beneficial for the patient with coronary artery disease. Hormonal changes mediated via the hypothalamosympathoadrenal axis occur. In the present study we looked for changes in circulating levels of norepinephrine, epinephrine, renin activity, and growth hormone as indicators of hormonal response to two stimuli—tracheal intubation and median sternotomy. The increases in plasma levels in epinephrine, norepinephrine, and renin activity normally seen in response to stressful stimuli were not seen in either group in this study. There was no significant increase above control levels in epinephrine, norepinephrine, or renin activity after intubation or sternotomy in either group. This might imply that both anesthetic techniques interfered with sympathetic tone to the same extent. More likely, however, it was the use of propranolol in these patients that was responsible for the lack of changes in levels of epinephrine, norepinephrine, and renin activity. Sebel (1) found no significant change in levels of norepinephrine or epinephrine following intubation and sternotomy in a comparable group of patients given 60 μg/kg of fentanyl for anesthesia. However, his group of patients received their last dose of beta-adrenergic antagonist the night before surgery.

Growth hormone levels were significantly higher after intubation and sternotomy in patients given halothane than they were in patients given fentanyl. Fentanyl in a dose of 50 μg/kg given for gynecologic surgery has been shown to interfere with the normal increase in growth hormone levels associated with surgery and anesthesia (19). Our results agree with this finding, a finding which may be common to all narcotics used in anesthetic doses. A similar interference with the normal increase in growth hormone levels associated with cardiac anesthesia and surgery has been described with anesthetic doses of morphine (20).

As the release of growth hormone is governed by the hypothalamus, a region possessing a large number of opiate receptors, it is possible that occupation of these receptors by fentanyl may interfere with the appropriate releasing factor for growth hormone. The significance of this interference with the normal increase in plasma levels of growth hormone associated with stressful stimuli is not known.

Finally, two of our patients given fentanyl had recall of the sternotomy and spreading of the chest with the sternal retractor despite administration of twice the dose (150 μg/kg) of fentanyl that Sebel et al (21) demonstrated to cause satisfactory depression of the electroencephalogram for purposes of anesthesia (50 to 75 μg/kg). Awareness with high-dose fentanyl has been reported (22). We wonder whether this may be related to the rapid decrease in plasma fentanyl levels that occurs after bolus administration (23). Possibly, awakening can occur at higher plasma levels than are associated with initial loss of consciousness, as seen with barbiturates. Lunn et al (24) reported loss of consciousness after 18 ± 4 μg/kg of fentanyl given intravenously corresponding with a plasma fentanyl concentration of 34 ± 7 ng/ml. Our mean plasma fentanyl concentrations at the time of sternotomy were 33 ± 6 ng/ml.

In conclusion, we have demonstrated several important differences between high-dose fentanyl and halothane as anesthetic techniques for cardiac surgery. However, we were unable to confirm significant hemodynamic or hormonal advantages of fentanyl reported by other investigators using 60 to 70 μg/kg of fentanyl for cardiac anesthesia despite the fact that we used 150 μg/kg of fentanyl.

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Tissue Oxygenation in Clinical Medicine: An Historical Review

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THE PHYSICAL separation of cells from the atmospheric gases is a necessary consequence of increasing bulk and cellular organization in organisms. In simple aerobic species, which rely on diffusion from the body surface to supply oxygen to internal cells, the diffusion distance for oxygen may be a powerful determinant of attainable size (1). This is due, of course, to the fact that the quantity of oxygen available at the cell membrane of an internal cell (Fig 1) is a function of its distance from the body surface, as described by Fick's law of diffusion

$$\dot{v} \text{ gas} \propto \frac{AD}{T} (P_1 - P_2)$$

where $\dot{v}$ = the rate of gas transport, A = the surface area of the body, T = the distance from body surface to the cell membrane of an internal cell, D = the diffusion coefficient of the medium, P_1 = the partial pressure of oxygen at the body surface, and P_2 = the partial pressure of oxygen at the cell membrane of an internal cell. As P_1, A, and D are usually fixed, it is apparent that as T increases, the rate of gas transport can be maintained only by virtue of a decrease in P_2. As the rate of gas transport from the cell membrane to the cell interior and mitochondria depends on the gradient ($P_2 - P_3$), a low value for P_2 necessarily limits maximum cellular gas transport, even if P_3, the intracellular oxygen pressure, should approach zero.

It should be noted that, in this analysis, the diffusion path T is considered to be nonmetabolizing, and therefore P_3 is linearly related to T at a constant gas transport rate (Fig 2, A). In living multicellular organisms, T is composed of actively metabolizing cells, the effect of which is to cause P_3 to decrease precipitously with increasing T. The relationship of P_3 to T in this instance is more nearly hyperbolic (Fig 2, B).

In larger, more complex organisms, particularly those of high metabolic activity, diffusion from the body surface, as the sole mechanism for gas transport, is inadequate. The development of these organisms, including man, has depended on the emergence of systems for the mass transport of gas, a principle function of which is to reduce the diffusion distance between the atmosphere and cells. In normal resting man, for example, the maximum diffusion distance for a molecule of oxygen may be in the range of 45 to 80 μ, based on the sum of the distances from alveolar surface to pulmonary capillary and from systemic capillary to a point in tissue midway between adjacent capillaries. The diffusion distance may be reduced further by increasing tissue capillary density, a phenomenon seen in animals acclimatized to high altitude environments (2) and known to occur with muscular contraction during exercise (3). Theoretically, an increase in capillary density would be expected to be a valuable adaptive response in a variety of disease states (4), but whether this occurs in man is unknown.

Maintenance of small effective diffusion distance depends, of course, on convection of gas to the proximal diffusing surface, by the bellows action of the lung, and on the circulatory transport of oxygen from the proximal diffusion surface (lung) to the distal
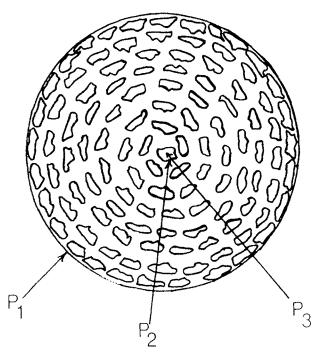
Fig 1. Spherical animal model. P_1, P_2, and P_3 represent partial pressure of oxygen at surface of animal, at membrane of an internal cell, and in interior of an internal cell, respectively.
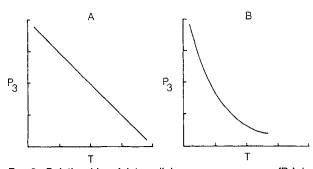
Fig 2. Relationship of intracellular oxygen pressure (P_3) to diffusion distance for oxygen (T). A, Relationship in a nonmetabolizing medium; B, oxygen-metabolizing tissue.

diffusion surface (systemic capillary). Another function of the respiratory mass transport system is to provide oxygen to the capillary diffusion surface in a quantity sufficient to support cellular oxygen consumption. To facilitate this, specialized oxygen transport proteins, such as hemoglobin, are utilized by most complex vertebrates. Of fundamental importance, however, is the fact that the quantity of oxygen available to the capillary surface is only indirectly related to tissue oxygen transport. By analogy, in simple organisms whose gas transport depends on surface diffusion, as discussed above, the adequacy of cellular oxygenation depends, clearly, on factors other than the nearly infinite quantity of atmospheric oxygen available for diffusion. For adequate tissue oxygen

exchange to occur, oxygen must be made available at sufficient partial pressure to promote diffusion into the tissue mass.

A discussion of gas transport in simple species may seem somewhat irrelevant as an introduction to the topic of tissue oxygenation in clinical medicine. However, as specialized mechanisms for the active transport of oxygen are not known to have evolved in mammals (1), the kinetics of tissue gas exchange in man remains governed, primarily, by the same physical laws of diffusion that regulate gas transport in less developed species. As will become apparent, these physical laws of diffusion remain the foundation on which the most advanced computer models of tissue oxygenation have been developed.

The intent of this paper is to examine commonly used indices of tissue oxygenation, in regard to their historical origins and utility in clinical medicine. Tissue P_{O_2} electrodes will not be discussed, however, as their use has been the topic of several recent reviews.

Clinical Estimation of Tissue Oxygenation

Concepts of Oxygen Availability as an Index of Tissue Oxygenation

The early work of Pflüger (5) and Warburg and Kubowitz (6) demonstrated that, in isolated tissue, cellular oxygen consumption is normally not limited or regulated by oxygen availability (Pflüger's law) (7). Similarly, in resting man, the quantity of oxygen available to tissue is, except perhaps in the heart, in great excess of that required to sustain the oxygen consumption of the tissue, which clearly is controlled by other factors. It is intuitive, however, that with progressive failure of the mass transport of oxygen in disease states, limitation of oxygen supply must eventually lead to inadequate tissue oxygenation. The essence of the problem in clinical medicine is to define the point at which failure of tissue oxygenation has occurred. Because total body tissue P_{O_2} cannot be measured directly, indices of respiratory mass transport failure have been sought.

The concept of total oxygen availability, the product of cardiac output and arterial oxygen content ($\dot{Q}t \times Ca_{O_2}$) was developed by Lauson and introduced by Richards (8) in 1944. Subsequently, many authors have used this term in discussions of tissue oxygenation, whereas others have proposed "flux" O_2 (9), "oxygen delivery" (10, 11), and "oxygen transport" (12) to refer to ($\dot{Q}t \times Ca_{O_2}$). Oxygen availability represents the total quantity of oxygen delivered to tissue per unit time and presumably available for

metabolism. As $\dot{Q}t$ and CaO_2 are relatively easy to measure in intensive care settings, oxygen availability is commonly used as an index of performance of the cardiorespiratory mass transport system and, indirectly, of tissue oxygenation. In patients with acute respiratory failure receiving continuous positive-pressure ventilation, for example, maximization of oxygen availability has been stated to be the therapeutic goal (13). The primary goal of therapy in all hypoxemia states is, however, the prevention of tissue hypoxia, and, although several authors have suggested that oxygen availability is the most important determinant of tissue oxygen tension (14, 15), the relationship of oxygen availability and tissue oxygenation is by no means straightforward. In other words, one may not assume that tissue oxygenation is adequate simply because a normal value of oxygen availability has been measured. The reasons for this are 2-fold: First, as discussed previously, tissue oxygenation is dependent on the partial pressure of capillary oxygen, tissue capillary density, and tissue oxygen consumption, and is related only indirectly to the quantity of oxygen available. As shown in Fig 3, equivalent values of oxygen availability may provide oxygen to capillaries at vastly different partial pressures, with predictably different effects on tissue oxygenation. Tissue anaerobiosis has been shown to occur, for example, with smaller decreases in oxygen availability during pure hypoxemia than when cardiac output is decreased (15). Second, the concept of oxygen availability ignores alterations in the distribution of oxygen at the tissue level which arise in a variety of disease states, particularly hemorrhagic and septic shock (16–18). Due to an increase in the effective diffusion distance for oxygen in these conditions, severe tissue hypoxia may coexist with normal or elevated values of oxygen availability.

The notion that high or normal values of oxygen availability may not always be equated with adequate tissue oxygenation has been supported by clinical studies. Shoemaker et al (19) have shown that although high values of oxygen availability may identify those patients who will survive early postoperative circulatory shock, survival during the middle and late stages of shock is nearly independent of oxygen availability. Similarly, in patients recovering from surgery for portal hypertension (20), oxygen availability may correlate negatively with prognosis, the patients with higher oxygen availability values exhibiting a higher mortality.

In light of the above, the term oxygen availability, as applied to the expression ($\dot{Q}t \times Cao_2$), may be
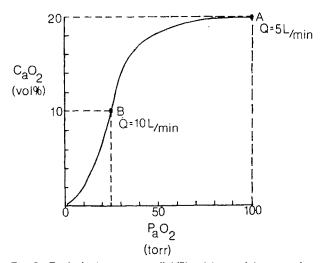
Fig 3. Equivalent oxygen availability at two points on oxyhemoglobin dissociation curve. Oxygen availability ($\dot{Q}_t \times Cao_2$) is identical in conditions A and B. Partial pressure of oxygen entering tissue capillaries, however, is 100 torr in situation A, and 25 torr in B.

misleading, as a variable fraction of the oxygen supplied per unit time may be actually "available" for metabolism. The term oxygen delivery, as used by Bendixen and Laver (10) and Mithoefer et al (11), may, therefore, be more appropriate, and will be used in reference to ($\dot{Q}t \times Cao_2$) in the remainder of this paper.

Despite its limitations, determination of oxygen delivery is a valuable procedure in intensive care medicine. The finding of a low value of oxygen delivery is particularly significant, as it identifies a potential cause of tissue hypoxia which is often remediable.

Concepts of "Corrected" Oxygen Delivery

Attempts have been made to modify the concept of oxygen delivery to improve its suitability as an indicator of oxygen transport and tissue oxygenation. Bryan-Brown et al (21), for example, have developed the idea of "consumable oxygen." Consumable oxygen is defined as ($\dot{Q}_t \times$ consumable Cao_2), where consumable $Cao_2 = Cao_2$ minus the content of oxygen existing at a Po_2 of less than 20 torr. (The content of oxygen below 20 torr is obtained with the pH, Pco_2, and hemoglobin concentration adjusted to values measured in mixed venous blood.) The content of oxygen delivered at a Po_2 of less than 20 torr is considered by Bryan-Brown et al (21) as unavailable for diffusion into tissue. This assumption is based on observations that unconsciousness ensues when the cerebral venous Po_2 falls below 20 torr (22), and that

oxygen consumption may decrease and anaerobiosis begin when oxygen delivery is acutely lowered to produce venous P_{O_2} values of less than 20 torr in canine muscle preparations (23). Bendixen and Laver (10), similarly, have utilized this concept in the development of the term oxygen reserve, defined as the normal venous oxygen content minus the venous content at a critical P_{O_2} of 20 to 30 torr. The validity of the assumption that oxygen at a P_{O_2} of less than 20 torr is not metabolizable, when applied to mixed venous blood in man, however, remains uncertain, especially when redistribution of blood flow has occurred, as in hypotension or exercise. Nevertheless, the concept of consumable oxygen is an important one, since it emphasizes the point that tissue oxygenation is more a function of capillary P_{O_2} than oxygen delivery. As with oxygen delivery, a normal value of consumable oxygen does not ensure adequate tissue oxygenation, because although it is numerically normal, the consumable oxygen quantity may be inappropriate relative to tissue demand. In addition, tissue hypoxia resulting from maldistribution of capillary blood flow will not be predictable from measurement of consumable oxygen. Correlation between calculated consumable oxygen delivery and survival or anaerobiosis in the intensive care setting has not been firmly established.

Mixed Venous P_{O_2} as an Index of Tissue Oxygenation

The supposition that the P_{O_2} of venous blood might reflect tissue P_{O_2} was first made by Barcroft in 1938 (24). In order to establish a relationship between venous P_{O_2} and mean tissue P_{O_2}, however, one must first determine what mean tissue P_{O_2} should normally be. One of the earliest physiologic approaches to this problem was developed by Verzar (25), who attempted to define the tissue P_{O_2} in salivary glands and muscle. Beginning with a simplified diffusion equation $(Q = d(P - p))$ (where Q = the O_2 uptake of the organ; d = the diffusion coefficient for oxygen; P = an estimate of mean capillary P_{O_2}, derived from the arithmetic mean of the arterial and venous oxygen saturations; and p = the oxygen pressure in the tissue), Verzar reasoned that if tissue P_{O_2} (p) were zero or nearly so, a decrease in mean capillary P_{O_2} (P) produced by lowering the $F_{I_{O_2}}$ of the animal being studied, would necessarily reduce the organs' oxygen uptake (Q). If p were substantially above zero, a decrease in capillary P_{O_2} (P) would be accompanied by a decrease in tissue P_{O_2} (p), with preservation of both the gradient $(P - p)$ and tissue oxygen uptake.

In the salivary gland, Verzar found that mean capillary P_{O_2} could be decreased by as much as 45 torr with no significant change in glandular oxygen uptake, suggesting that in the salivary gland, tissue P_{O_2}, initially, must have been at least 45 torr, a value nearly equal to that measured in the venous blood. In the gastrocnemius muscle, however, a decrease in oxygen uptake was seen with even moderate reductions in calculated mean capillary P_{O_2}, indicating that resting muscle tissue P_{O_2} must be low or zero. As the muscle venous P_{O_2} was 41 torr, venous P_{O_2} did not seem to reflect absolute tissue P_{O_2} in skeletal muscle. Although Verzar's equation certainly oversimplified the nature of tissue gas exchange, his experiments led to the consideration that venous P_{O_2}, a priori, might not provide an index of mean tissue P_{O_2} in every organ. Equally as important, his observations pointed to an apparent paradox in muscular gas exchange, because if muscle tissue P_{O_2} was nearly zero at rest, there seemed to be no plausible way to increase the capillary-to-tissue oxygen gradient and oxygen uptake of this tissue, a phenomenon known to occur in exercise.

In a further effort to define whether muscle tissue P_{O_2} was of a largely positive or nearly zero value, Erlang, at the request of Krogh (26), developed a more sophisticated diffusion equation, based on a theoretical model of tissue capillary gas exchange:

$$T_0 - T_x = \frac{p}{d}\left(\tfrac{1}{2}\,R^2\log_{NAT}\frac{x}{r} - \frac{x^2 - r^2}{4}\right)$$

where T_0 and T_x represent the partial pressures of oxygen at the center of the capillary and at any point within the tissue cylinder, respectively, p = the oxygen consumption of the tissue cylinder, and d = the diffusion rate for oxygen. Distances r, R, and x refer to the capillary radius, the tissue cylinder radius, and the distance from center capillary to any specific point within the cylinder, respectively. In this model, a circular tissue cylinder is supplied by a single central capillary, and the Krogh-Erlang equation allows the calculation of tissue P_{O_2} at any point within the tissue cylinder. R, the radius of the tissue cylinder supplied by the central capillary, was set at 15 μ, a value obtained from the direct counting, in vitro, of tissue capillaries after India ink perfusion of gastrocnemius muscle. This corresponds to a capillary density of $1350/mm^2$, an extremely high value, which may have been due to Krogh's treatment of the preparation with nitrates. With this capillary density, Krogh (26) calculated that the tissue P_{O_2} in muscle, at any point in the tissue cylinder, must be equal to or greater than the P_{O_2} of the venous blood. This conclusion was startlingly different from that of Verzar (25), and led

Krogh to reconsider his methodology and preparation.

In a subsequent investigation, Krogh (27) examined muscle capillary density in vivo, both at rest and during contraction of the muscle. At rest, muscle capillary density was found to be significantly less (mean 128 capillaries/mm^2) than that which he had observed in vitro, corresponding to a much larger tissue cylinder radius (R) of 65 μ. With such large tissue cylinders, Krogh deduced that, at rest, muscle tissue Po_2 must be extremely low, as Verzar (25) had previously surmised. As the partial pressure of oxygen in the venous blood of muscle was relatively high (i.e., approximately 30 torr) venous Po_2 did not seem numerically to reflect tissue Po_2 in resting muscle.

The finding of a low value of tissue Po_2 in resting skeletal muscle must have led to considerable speculation on the mechanism responsible for the large increases in muscular oxygen uptake during exercise. Clearly, increased oxygen uptake could not arise from a decrease in tissue oxygen partial pressure (with resultant increase in the oxygen pressure gradient (P_1 − P_2) for diffusion), as tissue oxygen pressure was nearly zero to begin with. This being the case, the only conceivable way to increase oxygen uptake during exercise (excluding active oxygen transport) would be to increase tissue capillary density, leading to a reduction in average tissue cylinder radius and effective diffusion distance. The opening of new capillary beds during exercise was directly observed in guinea pig muscle, with R decreasing from 65 μ at rest to 11 μ with work, accompanied by a 10-fold increase in muscular oxygen uptake. Although not measured by Krogh, one can reasonably assume that venous Po_2 decreased during muscular work.

The significance of these early observations, in terms of a relationship between venous Po_2 and tissue Po_2 may be summarized as follows: (a) In certain tissues, such as the salivary gland, venous Po_2 may accurately reflect tissue Po_2 regardless of the state of metabolism of the tissue; (b) In tissues like muscle, venous Po_2 may not be numerically equivalent to tissue Po_2 at rest, and changes in tissue capillary density may occur in response to alterations in tissue metabolism, the effect of which is to obscure a relationship between venous Po_2 and tissue Po_2. Thus, alteration in the distribution of oxygen in tissues may complicate the simple notion that changes in venous Po_2 must reflect changes in tissue oxygenation.

Krogh's model of diffusion of oxygen into tissue was further developed by Hill (28) in 1928, and by Kety (29) in 1957. These authors sought to define determinants of tissue oxygenation in general, how-

ever, and their studies were not directed specifically toward examining a relationship of venous Po_2 to tissue Po_2. In fact, it was not until 1974 that the first rigorous theoretical study of the relationship of venous Po_2 to tissue Po_2 was published by Tenney (4). Tenney's model, a refinement of the Krogh tissue cylinder model, allowed for the calculation of venous Po_2 and mean tissue Po_2 not only in the normal state, but during conditions of altered oxygen consumption, blood flow, hemoglobin concentration, and combinations of the above (Fig 4). With the reasonable assumption that capillary oxygen content decreases linearly from the arterial end to the venous end, the mean capillary oxygen content and Po_2 could be calculated. Mean tissue Po_2 was calculated by integrating the Krogh-Erlang equation between zero and R, the tissue cylinder radius, in a plane situated at the level of the mean capillary Po_2. The relationship of mean tissue Po_2 to venous Po_2, under a variety of conditions, could then be examined. An important finding of this study was that, although venous Po_2 might numerically overestimate or underestimate mean tissue Po_2 in various circumstances, changes in venous Po_2 were directly, and essentially linearly, related to changes in mean tissue Po_2 regardless of the conditions specified. Thus, this advanced model lends support to the general notion that changes in the venous Po_2 may be valuable in predicting changes in tissue oxygenation. Moreover, the model defines the critical nature of tissue capillarity as a determinant of tissue Po_2.

Clinical Usage of Mixed Venous Po_2

Since the early 1970s, the Po_2 of mixed venous blood has been used by clinicians as the basis for the estimation of tissue oxygenation in disease. The widespread acceptance of this notion may be revealed by a sampling of the literature:
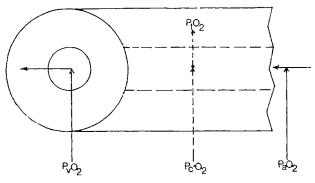
FIG 4. Tissue cylinder model with central capillary. Pao_2 and Pvo_2 are partial pressures of oxygen in arterial and tissue venous blood, respectively. $Pc'o_2$, mean capillary Po_2; Pto_2, mean tissue Po_2.

1. "... the fact that PO_2 in mixed venous blood remained unchanged indicates that the tissue oxygenation on the whole did not suffer..." (30).
2. "... since mixed venous oxygen tension reflects total body tissue oxygen tension..." (31).
3. "$P\bar{v}O_2$ is interpreted as reflecting the state of whole body oxygenation..." (11).
4. "Venous oxygen tensions and saturations can be measured as a reflection of tissue oxygenation..." (32).
5. "A $P\bar{v}O_2$ greater than 30 mm Hg usually reflects adequate tissue oxygenation..." (33).

Interestingly enough, statements such as these did not arise as conclusions drawn from a large number of well controlled clinical studies. More likely, they were based on an acceptance of the theoretical arguments that the oxygen in tissue is in equilibrium with that in venous blood. A few clinical studies do, however, support a relationship between mixed venous oxygenation, survival, and, presumably, tissue oxygenation. Nicotra et al (34), in examining the effects of positive end-expiratory pressure (PEEP) in patients with respiratory failure, found that "an increase in mixed venous oxygen content during PEEP seemed to impart a good prognosis," and in a recent study of patients with respiratory failure, Springer and Stevens (35) found survival to be less likely in those with low mixed venous P_{O_2}, irrespective of the particular value of Pa_{O_2}.

These observations are compatible with the theoretical predictions that a low mixed venous P_{O_2}, in certain instances, may coexist with (and indicate) tissue hypoxia. On the other hand, mixed venous hypoxemia need not always be associated with tissue hypoxia. Exercise in normal humans, for example, at levels well below the anaerobic threshold, is accompanied by rather pronounced decreases in mixed venous P_{O_2} (36). In this instance tissue oxygenation is preserved by an increased muscle tissue capillarity. As the state of tissue capillarity is unknown in most disease states, the exact value of $P\bar{v}_{O_2}$ at which tissue hypoxia becomes manifest, particularly in chronic hypoxemic states, is unclear. All that may be said for certain is that a decreasing mixed venous P_{O_2} in a particular patient, as a result of a disease process or therapeutic intervention, in the absence of circulatory redistribution, and with a constant rate of oxygen consumption, will be accompanied by a decrease in average tissue P_{O_2}.

The hallmark of a large number of diseases is redistribution of the systemic circulation. Well known examples include septicemia, due to either Gram-negative (16) or Gram-positive (37) organisms; hem-

orrhagic shock; cirrhosis of the liver (38); Paget's disease of bone (39); beriberi heart disease (40); various febrile states; and congestive heart failure. Redistribution of the circulation may result from abnormal flow rates through normal capillary beds in certain organs, or from the opening of arteriovenous anastomoses (36). Additionally, arterial blood may be distributed to the venous circulation by traversing areas of tissue whose oxidative enzymes have been blocked or are only partially functional. The functional shunting of arterial blood to the venous circulation, by any of these mechanisms, i.e., arterial admixture, is analogous to venous admixture in the lung. Just as the magnitude of pulmonary venous admixture is an important determinant of the arterial P_{O_2}, arterial admixture in the systemic circulation will have profound effects on mixed venous oxygenation. This concept may be further analyzed using a two-compartment model of the systemic circulation, as shown in Fig 5. Total oxygen delivery ($\dot{Q}_T \times Ca_{O_2}$) is divided peripherally into two fractions: tissue oxygen delivery ($\dot{Q}_C \times Ca_{O_2}$) and oxygen delivery to arteriovenous shunts ($\dot{Q}_s \times Ca_{O_2}$). The relationship of oxygen delivery to $C\bar{v}_{O_2}$ and mixed venous P_{O_2} in a system with a normal peripheral circulation ($\dot{Q}s = 0$) is shown in Fig 6. As oxygen delivery decreases, mixed venous P_{O_2} decreases and, conversely, as oxygen delivery increases, mixed venous P_{O_2} increases. In this normal
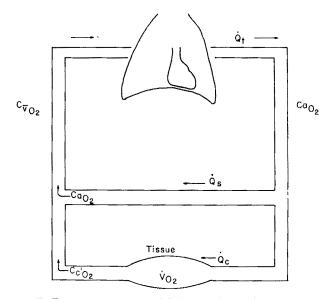
FIG 5. Two-compartment model of systemic circulation. $\dot{Q}$, cardiac output; $\dot{Q}_s$, blood flow shunted from arterial to venous circuit; $\dot{Q}_o$, tissue capillary blood flow; Ca_{O_2}, arterial oxygen content; $C\bar{v}_{O_2}$, mixed venous oxygen content; Cc'_{O_2}, oxygen content of blood leaving tissue compartment. As all oxygen consumption ($\dot{V}_{O_2}$) occurs in tissue compartment, blood leaving shunt compartment has composition of arterial blood.
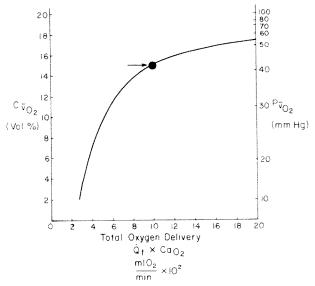
FIG 6. Relationship of total arterial oxygen delivery to mixed venous P_{O_2} ($P\bar{v}_{O_2}$) and oxygen content ($C\bar{v}_{O_2}$). All values are calculated with Fick equation, assuming mixed venous P_{CO_2} 46 mm Hg, pH 7.36, temperature 37°C, hemoglobin 15 mg/100 ml, and oxygen consumption 250 ml/min. Normal values of $C\bar{v}_{O_2}$, $P\bar{v}_{O_2}$, and total oxygen delivery are indicated by arrow.

FIG 7. Effect of increasing arterial admixture ($\dot{Q}s/\dot{Q}c$) on mixed venous and tissue end-capillary P_{O_2} at constant rate of oxygen delivery. With moderate arterial admixture, tissue-end capillary P_{O_2} decreases, whereas mixed venous P_{O_2} remains constant. When oxygen consumption decreases (large arrow) mixed venous P_{O_2} increases, whereas tissue end-capillary P_{O_2} remains at constant, low value. [particular values of tissue end-capillary P_{O_2} and $\dot{Q}s/\dot{Q}c$ reflecting limitation of oxygen consumption are estimates (21–23)].

situation, in which mixed venous blood gases are dependent on blood coming only from normal tissue capillaries, mixed venous P_{O_2} may accurately reflect changes in tissue end-capillary P_{O_2} and, presumably, tissue oxygenation.

If systemic arteriovenous shunting exists, however, $C\bar{v}_{O_2}$ becomes dependent on blood emanating from both tissue and shunt compartments. Expressed algebrically: $\dot{Q}_t \times C\bar{v}_{O_2} = (\dot{Q}_c \times Cc'O_2) + (\dot{Q}_s \times Ca_{O_2})$ or $C\bar{v}_{O_2} = (\dot{Q}_c \times Cc'O_2) + (\dot{Q}_s \times CaO_2)/\dot{Q}_t$, where Cc'_{O_2} represents tissue end-capillary oxygen content. (Note that this equation is similar to that used in calculation of $\dot{Q}_s/\dot{Q}_t$ (or venous admixture) in two-compartment lung models. In a two-compartment model of the systemic circulation, arterial admixture cannot be calculated, owing to the fact that $Cc'O_2$ is dependent on the magnitude of tissue blood flow ($\dot{Q}_c$), whereas $Cc'O_2$ in the lung is independent of the rate of blood flow in the ideal compartment, and may simply be calculated from the alveolar P_{O_2}.) In Fig 7 the effect of increasing shunt flow (at constant $\dot{Q}$ and $\dot{V}_{O_2}$) on $C\bar{v}_{O_2}$ and mixed venous P_{O_2} is shown. Both $C\bar{v}_{O_2}$ and mixed venous P_{O_2} remain constant in the presence of arteriovenous shunting. The oxygen-rich blood entering the venous system from the shunt compartment is balanced by the decreased oxygen content of blood coming from the tissue compartment, with a resultant stability of mixed venous P_{O_2} and mixed venous O_2 content. Despite a constant

mixed venous P_{O_2}, however, the venous oxygen content from the tissue compartment (Cc'_{O_2}) decreases in proportion to the degree of shunt flow. Tissue P_{O_2} must, therefore, fall despite a normal mixed venous P_{O_2}.

It is intuitive that with progressive shunting of arterial blood, tissue oxygen delivery will limit $\dot{V}_{O_2}$. Further reduction in tissue oxygen delivery due to shunting will cause $\dot{V}_{O_2}$ to decrease proportionately. Consequently, Cc'_{O_2} will cease to fall, and will remain at a constant low value, independent of the degree of change in $\dot{V}_{O_2}$. The contribution of the arterial shunt will then increase $C\bar{v}_{O_2}$, and $P\bar{v}_{O_2}$ must rise.

Obviously, then, in the presence of significant arterial admixture, mixed venous P_{O_2} may seriously overestimate tissue oxygenation. In support of this concept, Miller et al (41) have shown serious anaerobiosis and lactic acidosis to develop in the presence of elevated mixed venous P_{O_2} values in patients with Gram-negative septicemia. In patients with cirrhosis and portal hypertension, postsurgical prognosis has been shown to be inversely related to mixed venous P_{O_2} (20), with high venous P_{O_2} values more likely being indicative of severe arterial admixture than adequate tissue oxygenation. Preliminary studies (42) with tissue oxygen electrodes in dogs during Gram-negative sepsis have also shown a poor correlation between mixed venous P_{O_2} and tissue P_{O_2}, with severe

tissue anaerobiosis developing despite a normal mixed venous P_{O_2}. Thus, in clinical medicine, the interpretation of a normal or high mixed venous P_{O_2}, as with normal or high values of oxygen delivery or consumable oxygen, must be made with caution.

Conclusions

None of the commonly utilized indices of tissue oxygenation will reliably reflect tissue oxygenation in all clinical settings, owing, principally, to problems arising from circulatory redistribution in disease. Low values of oxygen delivery, consumable oxygen, or mixed venous P_{O_2} can usually be interpreted as compatible with tissue hypoxia, particularily in the presence of shock or when signs of frank tissue anaerobiosis (lactic acidosis) exist. Normal or high values of oxygen delivery or consumable oxygen alone do not ensure adequate tissue oxygenation, even in the absence of circulatory redistribution, as they may be inappropriate to tissue oxygen demand, Normal or high mixed venous P_{O_2} may reliably reflect the state of tissue oxygenation if redistribution of the circulation has not occurred, as $P\bar{v}_{O_2}$ is dependent on both tissue oxygen consumption and tissue oxygen delivery. If significant arterial admixture exists, however, as in the setting of septicemia, prolonged hemorrhagic shock, or cirrhosis the mixed venous P_{O_2} may seriously overestimate the state of tissue oxygenation.

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CLINICAL
reports

J-Wire versus Straight Wire for Central Venous System Cannulation via the External Jugular Vein

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In 1974, we reported a technique for obtaining access to the central venous system utilizing the external jugular vein and a flexible angiographic wire catheter guide or J-wire (1). Since that report, more than 100,000 cannulations of the central venous system and pulmonary artery via the external jugular vein have been performed with a success rate of 80% to 95% (2). Since our initial report, the use of angiographic wire catheter guides by anesthesiologists and other physicians appears to have increased. During the past 5 years pulmonary arterial catheters for invasive hemodynamic monitoring have achieved widespread acceptance. The popularity of the pulmonary arterial catheter (Swan-Ganz) and the increased use of angiographic wire catheter guides for various vascular catheterization applications has led to the speculation that the J-configuration of an angiographic wire catheter guide may not be responsible for its ability to traverse tortuous vascular channels. The

flexibility of the end of the wire guide, be it straight or of the J-type, could be responsible for its vascular passage characteristics. Most introducer sheaths and dilators for passage of a pulmonary arterial catheter contain a straight angiographic wire catheter guide (with a flexible end) as an integral part of the apparatus. Additionally, unpublished personal communications regarding the efficacy of the straight wire in traversing the external jugular vein needed to be verified. There is a difference in cost between the straight wire and the J-wire (approximately $1.25 per wire) and thus a significant economical impact might be felt if the straight wire could be shown to be equivalent to the J-wire.

This study was designed to compare the J-wire with the straight wire in external jugular vein catheterization so as to ascertain which of these devices was best suited for external jugular vein catheterization (Figure).

Methods

Human Subjects Committee approval was obtained and 36 consecutive patients requiring central venous system cannulation were studied. If a selected patient did not have visible external jugular veins, the central venous catheter was placed using an alternate technique and the patient was removed from the study. Cannulation of either the right or left external jugular vein (Trendelenburg position) was accomplished with a 16- or 18-gauge, 6.35-cm over-the-needle Teflon apparatus utilizing sterile technique. After the external jugular vein was successfully cannulated, a 50-cm long, 0.089-cm (0.035-inch) diameter, straight angiographic wire catheter guide (Argon Medical Products, Inc., Athens, TX) was passed through the short Teflon catheter and manipulated until it was ascertained to be in the thorax. If the straight wire was successfully passed to an intrathoracic position, the short cannula was removed and a longer definitive central venous pressure (CVP) catheter inserted over the wire using
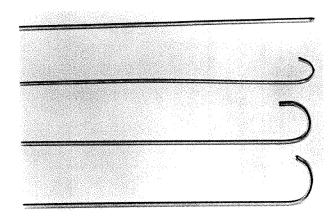
FIGURE. Four flexible angiographic wire catheter guides: top, wire of straight variety with flexible tip; lower three wires, J variety with varying radii of curvature.

it as a guide. If the straight wire could not be advanced into the thorax after 3 minutes of manipulation, it was removed and a flexible angiographic wire catheter guide with a 3-mm radius of curvature J (Argon Medical Products) (other dimensions the same as straight wire) was passed through the short catheter and manipulated until it was ascertained to be intrathoracic. The short catheter was then removed and a longer definitive CVP catheter passed over the J-wire.

After passage of the definitive catheter, the quality of the CVP reading was observed (fluctuation with respiration) and the ability to withdraw blood easily from the catheter was ascertained. All patients had postoperative chest roentgenograms to determine catheter position. Data were evaluated using the chi-square test and $p < 0.05$ was selected to represent statistically significant differences.

Results

The straight wire was successfully placed in an intrathoracic position and a catheter threaded over it in 16 of our 36 patients (44%). In instances where the straight wire could not be successfully passed into the thorax, the J-wire was subsequently successfully passed in all instances ($p < 0.05$). No complications occurred using either technique. Blood was easily withdrawn from all catheters and an acceptable CVP reading was obtained. Chest roentgenograms showed all catheters to be in the superior vena cava (Table).

Discussion

Our results indicate that the J-wire is superior to the straight wire for intrathoracic catheter placement via the external jugular vein. The fact that half of the

TABLE

J-Wire versus Straight Wire for External Jugular Central Venous Pressure Line Placement

External jugular vein placement attempts		Successful intrathoracic catheter placement	
		J-wire	Straight wire
Right	22	10 (100%)	12 (55%)
Left	14	10 (100%)	4 (29%)
Total	36	20 (100%)	16 (44%)

straight wires were successfully passed into the chest is somewhat intriguing as well as mystifying. This could be interpreted to mean that either the flexible end of the straight wire is beneficial in traversing tortuous vessels or that a number of patients have tortuosities not severe enough to require the J-configuration. We prefer to believe the latter of these two hypotheses is true. Success in passing the J-wire into the chest in the 20 instances where the straight wire failed certainly indicates a beneficial effect of the J-configuration. Because the straight wire was always attempted first, there is no way (in this study) of ascertaining how frequently the J-wire would have been unsuccessful if it had been used initially. It is possible that the success of the J-wire was due to information gained from the first attempt in passing the straight wire. We feel this explanation, however, is highly unlikely.

The beneficial effects of the J-wire are apparently explained by its lack of interaction with a vessel wall. The J-configuration "bounces off" or "rolls through" tortuous areas and sharp angulations in a vascular channel.

The J-wire is superior to the straight wire in navigating difficult vascular channels. When central venous system access is attempted utilizing the external jugular vein, we recommend utilizing an angiographic wire catheter guide with a J-tip configuration as this will result in a higher success rate. Because the J-wire appears to be superior to the straight wire in navigating vascular channels, it may be appropriate to utilize the J-wire in all situations of central venous system access where an angiographic wire catheter guide is desired.

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Bronchospasm during Cardiopulmonary Bypass

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Severe bronchospasm associated with hyperinflation of, and inability to deflate, the lung during and after extracorporeal circulation (ECC) is a rare complication, despite the fact that open heart surgery with cardiopulmonary bypass is now performed in more than 100,000 patients per year in the United States. Only one case of bronchospasm following ECC has been reported (1). Severe bronchospasm following thoracotomy, however, has been reported more frequently (2–5). The incidence of bronchospasm and massive lung collapse following general surgery was less than 0.2% in a series of nearly 29,000 operations reviewed by Waters (6).

In more than 10 years of experience with more than 1000 cases per year in our institution, bronchospasm during or following ECC was an unknown phenomenon. However, recently, two patients who underwent coronary artery revascularization had severe bronchospasm following ECC.

Case Reports

Case 1

In November 1980, a 51-year-old, 62-kg, 152-cm white woman was scheduled for a coronary artery bypass grafting. Significant past medical history was related to her coronary artery disease and hypertension. She had suffered an anterior myocardial infarction and repeated episodes of angina pectoris. She had mild orthopnea but no other symptoms of congestive heart failure.

There was a strong family history of coronary artery disease but no familial or personal history of bronchial asthma. She described an allergy to sulfonamides (hives). Her current medication included methyldopa, 500 mg/day, in divided doses; hydrochlorothiazide, 50 mg/day; diaze-

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pam 15 mg/day, in divided doses; nitroglycerin paste; and multivitamins.

Cardiac catheterization revealed extensive coronary arterial disease and akinetic inferior and apical segments of the left ventricle. The ejection fraction was 0.41 and pulmonary wedge pressure was 10 torr.

Preoperative medication consisted of morphine sulfate, 8 mg, lorazepam, 3 mg, and glycopyrrolate, 0.2 mg, given intramuscularly 1 hour before induction of anesthesia.

On arrival in the operating room, blood pressure was 130/80 torr, pulse rate 88 beats per minute, respirations 20 breaths per minute, and auscultation of the chest revealed no rales or wheezing. Two large peripheral intravenous cannulas were introduced, and a radial artery catheter was placed percutaneously before induction of anesthesia. Other monitoring devices included an electrocardiogram, a temperature probe, precordial and esophageal stethoscopes, and a central venous pressure catheter.

Anesthesia was induced with incremental doses of diazepam, 20 mg, and fentanyl, 1.75 mg, over a 15-minute period while administering 100% oxygen by face mask. Muscle relaxation was accomplished with pancuronium, 0.1 mg/kg, intravenously and tracheal intubation was performed with ease 2 minutes after topical spray of lidocaine, 160 mg, into the larynx and trachea.

Anesthesia was maintained with fentanyl (total 2 mg) and supplemental N_2O (0% to 50%) in oxygen. Ventilation was controlled using an Airshields ventilator delivering a tidal volume of 10 ml/kg at a frequency of 12 breaths per minute and with a peak inspiratory pressure of 18 cm H_2O. Arterial blood gas tensions were maintained within normal range. All hemodynamic variables remained stable until ECC was begun without incident. The priming solution consisted of 1000 ml of polyionic solution, 150 g of albumin, and 1 unit of packed cells. The cardioplegic solution consisting of 2000 ml of 5% glucose in Ringer's solution, 80 units of regular insulin, 40 mg of heparin, 60 meq of KCl, and 200 mg of $CaCl_2$. A Shiley blood bubble oxygenator was used and arterial perfusion pressure was maintained between 50 and 100 torr. The lungs were inflated statically at 5 cm H_2O of pressure with a flow of oxygen at 2 L/min. During the uneventful 120 minutes of ECC, three-vessel aortocoronary vein grafting was completed. At the time it was decided to terminate ECC the anesthetist's attempt to inflate the lungs met with high resistance. Inspiratory and expiratory wheezing was heard through the esophageal stethoscope. An inspiratory pressure of 60 cm H_2O was required to inflate the lungs; deflation was impossible. Hyperinflated lungs covered the margin of the sternum and stayed motionless. Investigation of the endotracheal tube including easy passage of a suction catheter ruled out the possibility of kinking or blockage of the endotracheal tube. Fiberoptic bronchoscopic examination ruled out the possibility of tracheobronchial tree occlusion by mucus or blood clots. Central venous pressure and left atrial pressure at this

time were 10 and 8 cm H₂O, respectively. There were no signs of pulmonary edema. A presumptive diagnosis of severe bronchospasm was made and treatment was instituted with intravenous injection of aminophylline, 250 mg, and methylprednisolone, 1 g. There was no noticeable improvement. Thirty minutes after the development of bronchospasm, 250 µg of epinephrine was administered intravenously. Perfusion pressure soared to 160 torr instantly. Within 5 minutes the lung gradually deflated, ventilation could be resumed, and perfusion pressure decreased to 80 torr. Heparin was reversed with protamine sulfate, 150 mg IV. Ventilation was controlled with the same ventilator with a peak inspiratory pressure of 28 cm H₂O. There was no further recurrence of bronchospasm during the remainder of the procedure or in the postoperative period. The patient was discharged 2 weeks later from the hospital in satisfactory condition.

Case 2

In February 1981, a 50-year-old, 70-kg 167-cm white man with a long history of hypertension and diabetes mellitus was incapacitated from angina pectoris despite medication with propranolol, 120 mg, isosorbid dinitrate, 120 mg, aspirin, 600 mg, and hydrochlorothiazide, 50 mg, daily. He had no symptoms of congestive heart failure. There was no personal or familial history of bronchial asthma. The patient had no allergies. Cardiac catheterization revealed three-vessel narrowing amenable to surgery; coronary angiography showed normal left ventricular function. He was scheduled for coronary revascularization.

One hour before surgery the patient received morphine sulfate, 10 mg, and scopolamine, 0.6 mg IM. On arrival in the operating room blood pressure was 150/90 torr, pulse rate 76 beats per minute, respirations 20 breaths per minute without wheezing on auscultation. After venous and arterial cannulation and institution of appropriate monitoring, anesthesia was induced with diazepam, 20 mg, and morphine sulfate, 35 mg, in incremental doses over a 15-minute period while 100% oxygen was administered by face mask. Muscle relaxation was obtained with 0.1 mg/kg of pancuronium. Two minutes before tracheal intubation 160 mg of lidocaine was applied topically to the trachea. Tracheal intubation was easily performed and anesthesia was maintained with 50% N₂O in oxygen (2:2 L/min). Ventilation was controlled with an Airshields ventilator delivering a tidal volume of 10 ml/kg at a frequency of 12 breaths per minute with an inspiratory pressure of 20 cm H₂O. Arterial blood gas tensions revealed satisfactory oxygenation and ventilation. One hour and fifteen minutes later ECC was begun; the lungs were inflated statically with oxygen at a pressure of 5 cm H₂O. Prime and cardioplegic solutions were the same as in case 1.

After 90 minutes of cardiopulmonary bypass and completion of coronary vein grafting, just before ECC was to be terminated, attempts to inflate the lungs met with great difficulty. The lungs gradually inflated but deflation was

impossible. Inspiratory and expiratory wheezing was heard through the esophageal stethoscope. Investigation of the endotracheal tube and trachea with a fiberoptic broncho-scope revealed no obstruction. Tracheal suctioning produced only a small amount of clear mucus; left atrial pressure and central venous pressure were 8 and 15 cm H₂O, respectively. A presumptive diagnosis of broncho-spasm was made and treatment was instituted with amino-phylline, 250 mg, and methylprednisolone, 1 g, given intravenously while ECC continued. The lungs gradually deflated within 10 minutes and ventilation became feasible. ECC was terminated, and there was no further recurrence of bronchospasm. The lungs remained compliant, and there was no wheezing for the remainder of the procedure and the postoperative period. The patient was discharged from the hospital 2 weeks later in satisfactory condition.

Discussion

In the two cases presented, bronchospasm was detected at the end of the bypass period when the first attempts to inflate the lungs met with resistance. Presumptive diagnosis of bronchospasm was possible on the basis of inspiratory and expiratory wheezing, high inflating pressure of the lungs with difficulty to deflate, normal left and right atrial pressures, and absence of tracheobronchial occlusion by the fiber-optic bronchoscopy. Because bronchospasm following thoracotomy (2–5), during cardiopulmonary by-pass (1) is rare, its sudden and unexpected occurrence surprised and intrigued us.

The cause of the bronchospasm described here is not precisely known. Likely causes include: (a) activation of C3a and C5a complement anaphylatoxins during cardiopulmonary bypass; (b) allergic reactions to various agents used for induction and maintenance of anesthesia, to various ingredients of priming and/or cardioplegic solution, and blood products used during bypass; and (c) light levels of anesthesia which produced reflex bronchiolar smooth muscle contraction.

Production of C3a and C5a complement-derived anaphylatoxins is known to occur in almost every patient having cardiopulmonary bypass (7). Anaphylatoxins stimulate the release of mast cell histamine, contract smooth muscle, and increase vascular permeability. It is well recognized that histamine release and bronchospasm are closely related even though anti-histamines have never been proven to prevent or reverse bronchospasm. Several observations implicate the pump oxygenator as a cause of complement activation during cardiopulmonary bypass (7). Duration of bypass has close correlation with the level of C3a and C5a complements. However, a causal relation

between the actions of the anaphylatoxins and bronchospasm has not yet been documented.

The two cases presented here occurred in a 3-month interval. However, drugs and materials used in the disposable bypass equipment did not differ in either case from those used routinely in other cases. Yet an allergic reaction to various agents used during the anesthetic and/or bypass periods cannot be ruled out.

In both of our cases, response to conventional treatment was satisfactory after the presumptive diagnosis were made. Treatment included the use of aminophylline, methylprednisolone, and epinephrine. Therapy with a strong beta-stimulating agent such as epinephrine in our first case should be undertaken only with caution in a patient with coronary artey disease. For this reason we continued ECC during administration of epinephrine (case 1), and until bronchospasm was relieved (case 2) to ensure proper balance of myocardial oxygen supply and demand.

In summary, this report presents bronchospasm as a rare complication of cardiopulmonary bypass. The possible causes of the bronchospasm are described and the appropriate management is suggested.

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Nitroglycerin Adsorption to Polyvinylchloride Seriously Interferes with Its Clinical Use

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Extemporaneous preparations of intravenous nitroglycerin solutions are currently being used in a number of centers to control intraoperative hypertension (1), severe aortic regurgitation (2), and hypertension in pregnancy during cesarean section (3), and for reduction of myocardial ischemia (4). A satisfactory injectable product may be prepared by using sublingual nitroglycerin tablets (5), nitroglycerin adsorbed onto lactose (6), or directly synthesized nitroglycerin (7). The material is dissolved in normal saline and the solution is sterilized by filtration.

With increasing use of intravenous nitroglycerin, a number of reports have been published describing apparent drug instability and binding to various intravenous containers and delivery sets. Several of these reports, however, provide conflicting data.

Our center has used nitroglycerin intravenously for approximately 8 years and over this period it has been noted that often the response to the drug seemed to be inappropriate in relation to the dose administered. To determine the cause of this inconsistent dose response, a series of in vitro experiments has been performed in an effort to reproduce the findings of published reports and to relate these to our experiences with this drug. During the course of these investigations we were able to document a clinical case in which nitroglycerin was administered using two different delivery systems and thus compare our in vitro findings to an in vivo situation.

Case Report

A 55-year-old man weighing 75 kg was seen in the

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emergency room with chest pain and shock, subsequently shown by electrocardiogram and enzyme levels to be due to an acute myocardial infarction. He was hypotensive and anuric and was immediately admitted to the intensive care unit where an intra-aortic balloon catheter was inserted through the common femoral artery to maintain his blood pressure.

The patient was given dopamine, 40 mg/hr, and nitroprusside, 6.6 μg/kg/min, to regulate his blood pressure. On day 4 the nitroprusside was replaced by nitroglycerin and the balloon catheter was removed. The nitroglycerin was initially given by a Sage (Sage Instruments, Division of Orien Research Inc, Cambridge, MA) pump through a polyethylene line (Cobe Laboratories, Lakewood, CO) at a dose of approximately 0.67 μg/kg/min. Response to this therapy was satisfactory, and the nitroglycerin dose remained relatively constant. The nitroglycerin administration was then switched to an Imed (Imed Canada Inc, Mississauga, Ontario, Canada) pump with polyvinylchloride administration lines (Baxter Travenol Laboratories, Malton, Ontario, Canada). The dose increased over 5 hours to a maximum of 8.8 μg/kg/min, but despite the increased dose the blood pressure became difficult to regulate. The administration of nitroglycerin was changed back to Sage administration with the polyethylene line on day 5, and subsequently the dose was decreased to a relatively constant rate of 1.12 μg/kg/min with an appropriate response (Figure). The nitroglycerin was discontinued on the following day.

Discussion

This patient's blood pressure was maintained reasonably well with both the polyethylene and the polyvinylchloride tubing, but the pressure was substantially more difficult to regulate when the polyvinylchloride set was used. This was reflected in the more frequent dosage adjustments required with the polyvinylchloride set. Blood pressure was equally well maintained with both the polyethylene and polyvinylchloride sets; this was probably due primarily to frequent dose adjustments when polyvinylchloride tubing was used (Table).

An evaluation of the dose required for blood pressure maintenance showed that the dose required to maintain the blood pressure with the polyethylene set was very different from that needed with the polyvinylchloride set (Table). This case demonstrates that when a polyvinylchloride set is used a dose approximately 10 times that used with a polyethylene set may be needed to achieve the same therapeutic response.

It has been shown that the loss of drug in polyvinylchloride plastic tubing is inversely proportional to
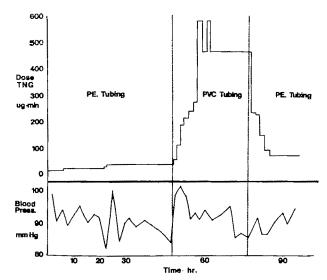
FIGURE. Nltroglycerin dose and blood pressure versus time and type of plastic. Blood pressure, diastolic values; PVC, polyvinylchloride; PE, polyethylene; TNG, nitroglycerin.

TABLE

Dose-Response Data for Polyethylene (PE) and Polyvinylchloride (PVC) Administration Lines

	Mean (±SD)	Significance*
Dose adjustments/24 hr		
PE	1.6 (—)	
PVC	8.0 (—)	—
Dose adjustment (μg/kg/min)		
PE	0.179 (±0.103)	
PVC	2.23 (±1.55)	$p < 0.001$
Blood pressure maintenance (mm Hg)		
PE	89.1 (±4.87)	
PVC	89.6 (±5.76)	NS
Maintenance dose (μg/kg/min)		
PE	0.485 (±0.319)	
PVC	5.13 (±2.609)	$p < 0.001$

* Determined by Student's t-test.

the flow rate (8, 9) and that the loss of drug is due to a sorptive process since the intact drug which had been lost could be recovered by elution with methanol (6). It has also been shown that the amount of nitroglycerin lost is directly proportional to the surface area of the polyvinylchloride plastic to which it is exposed (10). Nitroglycerin does not appear to be adsorbed by contact with polyethylene tubing (9), polyolefin containers (11), glass (12), or polypropylene (D. Cote and M. Torchia, unpublished data, 1981). Our own work, which was done to conform to the conditions under which the drug is used at this institution, agrees with these findings (unpublished data).

Two papers that reported on loss of nitroglycerin in glass and plastic intravenous containers showed that the concentration of drug declined exponentially with time in both types of containers (5, 13). This finding has not been substantiated by other workers

(6, 8, 9, 12, 14), and it should be noted that in one of these studies (13), samples for drug assay from the glass bottles were withdrawn through a short length of plastic tubing, the composition of which was not stated.

The mechanism of nitroglycerin loss in intravenous containers and lines has not yet been elucidated, although one series of kinetic and equilibrium studies has been published (15) and the foundation for a mathematical model describing this drug loss has been reported (16).

A recent publication suggested that the adsorbing sites on the administration set could be saturated before use (17). As the exact mechanism of drug loss is not known, the point at which drug loss becomes insignificant may vary considerably with different types of administration sets and containers (10). A potential hazard with presaturation is the fact that the bound drug can be eluted with methanol (6), a fact of importance inasmuch as several intravenous formulations for drugs with poor water solubility use a vehicle composed of propylene glycol, water, and ethanol, which presumably might also elute the nitroglycerin from the plastic tubing. Examples of these formulations include furosemide, digoxin, and phenytoin. If an administration line "saturated" with nitroglycerin were to be used for the bolus administration of one of those drugs, it is conceivable that a concomitant "bolus" of eluted nitroglycerin would be administered. Preliminary work in our laboratory supports this possibility.

It would appear that use of polyvinylchloride plastics should be avoided at any stage of the preparation, storage, or administration of intravenous nitroglycerin to prevent possible dosage inconsistencies.

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letters
TO THE EDITOR

A Potential Hazard of Thermodilution Injection

To the Editor:

Cardiac output measurement by thermodilution is widely used today. Hand-held, carbon dioxide-powered injectors increase the precision of these measurements. We report here a potential hazard of the OMP 3720 injector.

During an injection for a cardiac output determination, the injector stopped halfway through the injection. The syringe was removed to facilitate changing the CO_2 cartridge. The old cartridge was removed and a new one put in place. As soon as the new CO_2 cartridge was seated, the injector spontaneously fired and caught the operator's left ring finger between the plunger which drives the syringe and the distal end of the injector where the syringe barrel is held. It was impossible to release the plunger until we realized that the trigger on the injector was in the inject (down) position. As soon as the trigger was switched to the aspirate (up) position it was possible to free the finger. Fortunately, the operator suffered only soft tissue trauma.

We recommend that CO_2 cartridges be changed only when the switch is in the up (aspirate) position and that fingers be kept clear of the path of the injector plunger.

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Diazepam in an Oil Emulsion

To the Editor:

Pain and thrombophlebitis associ-
ated with the injection of diazepam seem to be less frequent and less severe when diazepam is dissolved in oil and emulsified in water than when dissolved in an aqueous vehicle with organic solvents (1).

We compared in a double-blind study the effects of diazepam dissolved in oil and the effects of an aqueous solution of diazepam dissolved in ethyl ether and glycofurolium.

It has been shown (2) that there is no significant difference between propylene-glycol and glycofurolium on local venous reactions.

Twenty consecutive patients (aged 35 to 75 years) undergoing elective gastroscopy were studied. Thirty minutes before endoscopy 10 to 20 mg of morphine and 0.15 to 0.3 mg of scopolamine hydromromide were given subcutaneously. Immediately before the gastroscopy a disposable Teflon cannula was placed in a vein on the back of each hand. Local anesthesia was applied to the throat and 7.5 mg of diazepam in oil and 7.5 mg of diazepam in aqueous vehicle were simultaneously injected in a double-blind manner into the two cannulas.

The patients were at once asked which hand, if either, had pain associated with the injection, followed by flushing of both catheters. If extravasation occurred the patient was excluded from the study. Four days later the veins were examined for redness, tenderness, and induration; if all three were present, thrombophlebitis was considered to be present.

The results were as follows: Eighteen patients reported that the administration of diazepam in an aqueous vehicle was more painful than diazepam in oil. No patients reported diazepam in oil more painful than diazepam in an aqueous vehicle and two patients reported that diazepam in oil was equally as painful in both hands as the other method or that there was no pain in either hand.

There were no cases of thrombophlebitis after diazepam in oil; there
were three cases of thrombophlebitis after diazepam in the aqueous solution.

The difference in the incidence of pain between the solutions was statistically significant ($p < 0.01$). The numbers of cases of thrombophlebitis were to low in this small number of patients to allow calculation of statistical significance.

Diazepam in oil emulsion has the same therapeutic effect when administered intravenously as it does when injected in an aqueous solution (3). The price in Denmark for diazepam in oil (Diazemuls) is approximately twice the price of the commonly used diazepam preparations. If this were not the case, we would routinely recommend the use of diazepam in oil emulsion as intravenous medication before endoscopy.

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Consistency of Action of Midazolam

To the Editor:

The recent paper by Samuelson and colleagues (1) and publications from the same department (2-4) and

LETTERS TO THE EDITOR

elsewhere (5–7) concern us, in that they suggest that midazolam is a satisfactory induction agent, comparable in consistency of action with thiopental. This has not been our experience in more than 500 administrations of this promising water-soluble benzodiazepine.

In initial volunteer studies (8) we found a great individual response to the drug, which was not related to the weight of the subjects. Subsequently we evaluated doses ranging from 0.15 to 0.50 mg/kg using a variety of premedicants (9). Here again we noted a wide variability in response, particularly in unpremedicated patients. As with diazepam, it often took up to 3 minutes from the end of injection for the full effect to occur. Narcotic premedication potentiated the sedative effect of midazolam. One important finding was the greater predictability of action and lower dosage requirements in the elderly. This has since been confirmed in pharmacokinetic studies where a greater initial volume of distribution and a longer terminal half-life was found in patients aged 60 years and older compared with a comparable group in the age range of 20 to 40 years (10). Even when using it in heavily premedicated patients scheduled for coronary artery surgery, such as in the series of Samuelson et al, we have not found it to be reliable in action.

An intravenous induction agent must be reasonably consistent in its action and preferably effective doses should induce anesthesia in one arm-brain circulation time (11). When injected rapidly in the period of forearm reactive hyperemia following release of an arterial tourniquet, effective doses of thiopental, methohexital, a number of other thiobarbiturates, Althesin (12), and minaxolone (13), will induce anesthesia in 10 to 13 seconds. The average time of onset of 4+ mg/kg of thiopental was 10.1 seconds, and this dose was effective in all of the 40 unpremedicated patients studied (13). We have measured the time from end of injection to induction in unpremedicated subjects given 0.3 mg/kg of midazolam during a period of reactive forearm hyperemia. Our findings (Table) confirm the lack of consistency of action of midazolam in the young, with a slower onset time than with thiopental.

TABLE

Effect of Midazolam (0.3 mg/kg) in Young and Elderly Patients*

Age	No. of patients	No. of patients asleep in 5 min	Av onset time
yr			sec
20–40	10	4	37.5
60+	7	7	23.6

* Drug was injected rapidly in a large forearm vein at the height of reactive hyperemia following release of arterial tourniquet.

In the light of these data we feel that midazolam is most useful as a sedative-hypnotic rather than as an induction agent. It has now been used for this purpose in more than 200 patients undergoing various dental procedures under local anesthesia or for endoscopy and has proved most valuable in this field.

We are at a loss to explain the difference between our findings and those of our American counterparts. It cannot be due to racial or environmental factors as at least one American author has noted this variability of action with midazolam (14). We do feel that a promising drug could get into disrepute if it is used for the wrong indications.

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To the Editor:

In response to the letter of Drs. Dundee and Kawar regarding consistency of action of midazolam: If one reads our pubications (1–6) carefully, it is clear that in only one have we actually compared midazolam with thiopental, and in that article (2) we stated, "There are some advantages to each drug. Thiopentone is more rapid and specific for induction of anaesthesia and midazolam is superior for maintenance." We have not only admitted that interindividual variability occurs with midazolam (2, 4, 5), but have actually tried to investigate the cause for this variability, relating it in part to differences in serum protein concentration (5). Another important variable that we (7) and Gamble et al (8) have shown is the influence on midazolam induction of premedication: the stronger the premedication, the more rapid the induction.

We would like to emphasize that midazolam is a 1,4-benzodiazepine. Benzodiazepines are versatile drugs. They have hypnotic, amnestic, anticonvulsant, anxiolytic, and muscle relaxant properties. Midazolam will be used not only for premedication and sedation during procedures but also for induction of anesthesia in some patients. It is superior to diazepam for induction of anesthesia (1, 6), the drug with which we feel it most properly should be compared as both are 1,4-benzodiazepines. Advantages of midazolam over diazepam are: greater water solubility (at pH <4.0) (7), less pain on injection (1), more rapid action (1, 6), less interindividual variation in response to a milligram per kilogram intravenous injection (1, 6), shorter duration of action (9), more rapid total body clearance (10, 11), and significantly shorter t½ α and t½ β (10, 11). Additional advantages of midazolam may include better intramuscular absorption and a lower incidence of thrombophlebitis. A possible disadvantage of midazolam compared with diazepam is that hypotension is more frequently encountered during induction with midazolam (6).

We agree with Dundee and colleagues that an induction agent must be reasonably consistent in its action, and we have found in our experience that when given in appropriate doses of 0.2 mg/kg over 5 to 15 seconds (4), that midazolam is "reasonably" consistent and reliable (1–6). We do not agree that an induction agent always "should induce anesthesia in one arm-brain circulation time" nor do we agree with the implication that rapidity of hypnotic action is the most important pharmacodynamic effect. Not all patients require induction in one circulation time; indeed, in order to ensure more than one circulation time in some patients, slower inductions are required. For example, in A.S.A. class III and IV patients it is often preferable to use a slower acting benzodiazepine such as diazepam, which produces significantly less cardiovascular depression, than the more rapidly acting thiopental (12). Also, there are many pediatric patients in whom an inhalation anesthesia induction is most appropriate.

In conclusion, we feel as we did in 1979 that "midazolam does not dethrone thiopentone (2) as king of the

anesthesia induction agents." However, it will probably become a more popular benzodiazepine than diazepam in the practice of anesthesia. Among induction agents, midazolam as a benzodiazepine will find a secure place alongside drugs of the barbiturate, phencyclidine, steroid, eugenol, and other classes. Each has unique pharmacologic properties which anesthesiologists have learned to rely on to accomplish the particular anesthesia induction indicated for an individual patient. We concur with the statement of a prominent investigator in this field who stated, "It is apparent that many intravenous agents are available to the anesthesiologist. It is hoped that a broader view of the potential of non-barbiturate anesthetics will be taken. Proper understanding and use of these drugs require the special skills of an anesthesiologist who, in this context, is truly an 'applied pharmacologist'" (13).

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Laser Fire Hazards

To the Editor:

Although we agree that there are fire hazards associated with the use of carbon dioxide lasers and that techniques that prevent fire hazards should be used, the article by Patel and Hicks (1) contains several errors of fact and interpretation that seriously interfere with the achievement of their goal.

The authors appear to imply that lower powered lasers are less dangerous than higher powered lasers. We feel that it is dangerous to draw conclusions relating the power of the laser to the time required to ignite an endotracheal tube. In principal, any laser capable of vaporizing tissue can immediately ignite an endotracheal tube if the beam is sufficiently well focused.

The recommendation that inspired oxygen concentrations be kept at 20% to 25% is in agreement with earlier studies. (2, 3) However, these earlier studies referred to oxygen in air and not nitrous oxide as nitrous oxide alone and in all combinations with oxygen readily supports combustion.

The recommendation that all metal surfaces used around the laser be "well buffed" contradicts the physical principles governing reflection of light from metallic surfaces. Nonspecular reflection of a focused beam (as from a matte surface) reduces the energy density of the beam. Thus, "well buffed" (mirror-like) surfaces should be avoided.

The statement that both "halothane and nitrous oxide are flammable" is simply untrue. The National Fire Protection Association defines a

flammable liquid as one having a flash point less than 37.8°C and having a vapor pressure at that temperature of less than 2068.6 torr. A combustible liquid is similarly defined as having a flash point greater than 37.8°C. (4) By these definitions neither halothane nor nitrous oxide is flammable or even combustible although nitrous oxide will support combustion.

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Aminophylline-Theophylline Drug Incompatibilities

To the Editor:

The review article on aminophylline (1) by Stirt and Sullivan was very thorough. However, we would like to point out an important area for the anesthesiologist that was overlooked, namely the potential physical and chemical incompatibilities when the theophylline in aminophylline is combined with other drugs.

Theophylline is a basic drug, with a pH between 8.6 and 9.0 (2). Optimum stability occurs at pH 8.0 and above. Crystals of theophylline will form below pH 8.0 but probably not unless the concentration is greater than 40 mg/ml. This incompatibility is therefore more likely to occur if certain admixtures are made in syringes or small volumes of fluids than if components are added separately to large volume intravenous fluids (2-4).

Because of the alkalinity of theophylline-containing solutions, drugs known to be alkali-labile should be avoided in admixtures. These include epinephrine HCl, levarterenol bitartrate, isoproterenol HCl, and penicillin G potassium (2, 3).

Published studies on compatibility have used physical and/or chemical incompatibility as their criteria. Physical or visual incompatibilities are typified by precipitation, effervescence, color change, turbidity, or cloudiness. Chemical incompatibility usually involves the degradation of drugs to produce therapeutically inactive or toxic products (2). Thus, it should be noted that incompatibility literature has several limitations, for example, lack of observable visual incompatibilities does not necessarily indicate chemical stability. Therapeutic incompatibilities are not usually addressed. In addition, most of the literature does not assess factors such as concentration, order of mixing, differing formulations of a drug made by different manufacturers, and the materials from which the containers are made (4).

The following is a list of drugs reported (2-11) to be physically or chemically incompatible when mixed with theophylline:

Antimicrobials
Amikacin sulfate
Cephalothin sodium
Cephapirin sodium
Chloramphenicol sodium succinate
Chlortetracycline HCl
Clindamycin phosphate
Erythromycin gluceptate
Nafcillin sodium
Novobiocin sodium
Oxytetracycline HCl
Penicillin G potassium
Sulfadiazine sodium
Sulfisoxazole diolamine
Tetracycline HCl
Vancomycin HCl

Analgesics/Anesthetics
Anileridine HCL
Anileridine phosphate
Codeine phosphate
Levorphanol bitartrate
Meperidine HCl
Methadone HCl
Morphine sulfate
Pentazocine lactate
Procaine HCl
Thiopental sodium

Adrenergics
Epinephrine HCl
Isoproterenol HCl

Tranquilizers/Antiemetics
Chlorpromazine HCl
Diazepam
Dimenhydrinate
Hydroxyzine HCl
Prochlorperazine edisylate
Promazine HCl
Promethazine HCl

Vitamins
Ascorbic acid
MVI-12
Vitamin B complex
Vitamin B complex with C

Intravenous Solutions
Fructose 10% in H_2O
Fructose 10% in NaCl
Invert sugar 10% in H_2O
Invert sugar 10% in NaCl

Miscellaneous
Cimetidine HCl
Corticotropin
Doxapram HCl
Hydralazine HCl
Insulin, regular
Methylprednisolone sodium succinate
Phenytoin sodium
Succinylcholine chloride

This list is by no means inclusive. We thus urge clinicians to check with the pharmacist if there is any question concerning the potential incompatibility of theophylline with other drugs.

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LETTERS TO THE EDITOR

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book REVIEWS

The Practice of Electrocardiography, by T. M. Blake, Garden City, NY, Medical Examination Publishing Co., Inc., 1980, 236 pp, $12.00.

The laudable goal of this short book is to take the interpretation of electrocardiograms (ECGs) away from the isolation of the ECG lab, where pattern recognition is the sine qua non, and move to the bedside where physiologic principles can be applied to individual patients with specific signs and symptoms. This goal, however, is only partially achieved.

Although this book is directed primarily toward medical students, the preface notes that there is something here for everyone, from laboratory technicians to practicing physicians. Trying to encompass this broad audience causes much of the problem. The first section describes, in a very elementary way, the electrical genesis of the ECG, and this is followed immediately by a more detailed look at vector analysis of the QRS complex and the T wave. The second section addresses mechanisms, including arrhythmias. In the third section, which deals with structure and function, the approach is somewhat unique and helpful for the beginner—QRS morphology indicating specific structural alteration (hypertrophy, infarction) with ST-T analysis reflecting functional or metabolic change (ischemia, electrolyte abnormality).

Unfortunately, the mechanism section is found wanting. The definition of each arrythmia is usually limited to a few short sentences with a marked paucity of accompanying ECG strips. Those that are present are black on gray, without formal explanation of format, and occasionally the legends are difficult to read. New terminology is also introduced—"usurping or default"—instead of the more familiar ectopic and escape.

The reference list is voluminous (699) and can direct the reader to a more detailed study, but it lacks organization, either by chapter, subject, or author.

I cannot recommend this book to the anesthesiologist looking for an introduction to electrocardiography. The early chapters are too basic (as they are meant to be), the latter ones too brief, and the discussion of arrythmias is inadequate for our needs.

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Occupational Hazards to Operating Room and Recovery Room Personnel, International Anesthesiology Clinics, Volume 19, edited by J. E. Cottrell, Boston, Little, Brown and Co., 1981, 183 pp, $40.00/yr.

The foreword to this book suggests that the reader will find answers to many troublesome questions, such as: Are the effects of very low concentrations of anesthetics on cell growth paralleled by the possibility of teratogenicity and carcinogenicity? If anesthetics at one concentration can render a patient unconscious, can far lower concentration impair the thought processes of exposed personnel? Is it possible to make an anesthetic that is totally risk-free? Is it too costly to install scavenging equipment in every anesthetizing location? How should the cost-benefit ratio of the use of these drugs be evaluated? Unfortunately, after reading this book, most of these questions remain unanswered as do the most pressing questions on the subject: Is working in the operating room hazardous at all and, if it is, is it because of contamination by waste anesthetic gases?

The book is of uneven quality. Some of the chapters, such as those dealing with cell replication, the British viewpoint on occupational hazards, and the effect of anesthetics on the immune system, clearly present what is known and what is not known about these subjects. The first chapter mentioned, by John Nunn, is an excellent summary containing the most current information regarding the effects of nitrous oxide on vitamin B_{12} metabolism and the possible consequences that this may have on the nervous system. Other chapters are less relevant. In one chapter, the authors acknowledge that there is little or no information regarding trace levels of anesthetics and the subject of their chapter, and then they go on to discuss studies in which anesthetizing concentrations were used—an unjustified and potentially misleading extrapolation. The most serious problem with the book, however, is its lack of balance. None of the chapters takes the point of view that the operating room may not be a hazardous location and, in fact, none systematically examines the epidemiologic data. These data have often been criticized and were, to begin with, the basis for the assumption that the operating room was an occupationally

hazardous location. In summary, except for the chapter by Nunn, this reviewer would not recommend this book.

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A Basis and Practice of Neuroanaesthesia, Second Edition, edited by E. Gordon, New York, American Elsevier Publishing Co., Inc., 1981, 354 pp, $87.75.

The second edition of this multiauthored monograph firmly establishes itself in the medical literature as an invaluable reference tool for all those involved in the care of the patient with central nervous system abnormalities. However, much repetition occurs throughout, and perhaps the monograph would have been more effective and to the point if it had included only the following: the chapter, "The Effects of Anaesthesia on Cerebral Metabolism"; the section, "Measurement and Regulation of Cerebral Blood Flow and Pathophysiology of Acute Brain Disease," without the subsection, "Anaesthetic Protection of Ischemic Brain," in the chapter, "Anaesthesia and Cerebral Blood Flow"; the sections, "Gradients of Intracranial Pressure," and "Monitoring of Intracranial Pressure during Anaesthesia," in the chapter, "The Influence of Anaesthetic Drugs and Techniques on Intracranial Pressure"; the sections, "Premedication," "Position of the Patient during the Operation," "Air Embolism," "Monitoring during Anaesthesia," and "Fluid and Blood Replacement during Operation and Emergence," in the chapter, "Anaesthesia for Neurosurgery"; and the chapters, "Anaesthesia for Neuroradiological Examinations," "Postoperative and Intensive Care," "Induced Hypotension," and "Induced Hypothermia." With the inclusion of only these

chapters, sections, and subsections, a more concise, nonrepetitive monograph would have been obtained.

The chapter, "The Neurophysiology of Anaesthesia" is well written and informative, but the introduction and section, "The Nature of Anaesthesia," plus the subsection, "Control of Consciousness," would more appropriately be found in a basic science text. The other section in this chapter would then be more valuable and clinically applicable if it had been titled, "Neurophysiologic Brain Monitoring," with each section and subsection written accordingly.

Discussion of specific central nervous system abnormalities such as hemorrhagic and ischemic disease, vasospasm, pituitary abnormalities, spinal cord abnormalities, etc, and recent advances in their management would have added to the book's value. Discussion of newer treatment modalities and techniques such as naloxone, dimethyl sulfoxide and thyrotropin-releasing hormone for the prevention of central nervous system ischemia, and the calcium channel blockers for deliberate hypotension would have stimulated the reader to look forward to the next decade.

The chapters by the editor are particularly well written as a result of seemingly sound clinical experience.

This monograph is a valuable resource for review reading, despite the repetition and lack of inclusion of some of the newer, more exciting advances.

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Adverse Reactions to Anaesthetic Drugs, edited by J. A. Thornton, New York, American Elsevier Publishing Co., Inc., 1981, 336 pp, $97.00.

This text is a scholarly work and should appeal to an international audience. It provides a complete source

of references on drug interactions and adverse reactions to anesthetics, especially those involving immunologic mechanisms. Referencing is extensive and complete through 1979, including many references in frequently overlooked journals.

The title of the text is somewhat misleading. A more appropriate title might have been "Immunologic Mechanisms and Adverse Anaesthetic Reactions," as approximately 50% of the text is devoted to this topic. The remainder consists of an extensive review of adverse reactions to neuromuscular blockers, a chapter on operating room pollution, and reviews of nonimmunologic drug interactions in anesthesia.

As is not unusual in a multiauthored text, there is often overlap in presentation. This is especially true for interactions involving the muscle relaxants that are extensively reviewed in one chapter and more briefly reviewed in others. The reader's task is made difficult by the fact that the index is incomplete and frequently omits drugs listed in the text.

The chapter discussing the immunologic mechanisms underlining halothane hepatitis is complete, but overlooks the controversy of whether halothane hepatitis is a significant clinical problem or, if so, whether it might result from direct hepatotoxicity from toxic metabolites.

The chapter on the effects of environmental pollution due to inhalation agents is excellent and is well referenced (to 1979) with a total of 122 citations.

In summary, Thornton has edited a monograph primarily dealing with immunologic mechanisms of anesthetic interactions with additional discussion of adverse reactions involving neuromuscular blocking agents and a review of operating room pollution. The text is exceedingly well referenced. The book should be of interest to those practitioners interested in immunology and its relationship to adverse responses to anesthetic agents.

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BOOK REVIEWS

BOOKS RECEIVED

Nurse Anesthetists' Continuing Education Review, by A. R. Bakutis, Garden City, NY, Medical Examination Publishing Co, Inc, 1982, 224 pp, $20.00.

Dictionary of Medical Ethics, edited by A. S. Duncan, G. R. Dunstan, and R. B. Welbourn, New York, The Crossroad Publishing Co, 1981, 459 pp, $24.50.

Recovery Room Care, edited by J. S. Israel and T. J. DeKornfeld, Springfield, IL, Charles C Thomas, Publisher, 1982, 334 pp, $37.50.

Manual of Cardiac Surgery, Volume II, by B. J. Harlan, A. Starr, and E. M. Harwin, New York, Springer-Verlag, 1981, 347 pp, $125.00.

Pulmonary Physiology, by M. G. Levitzky, New York, McGraw-Hill Book Co, 1982, 271 pp, $9.95.

Management of Medical Problems in Surgical Patients, by M. E. Molitch, Philadelphia, FA Davis Co, 1982, 795 pp, $40.00.

Respiratory Emergencies, Second Edition, by K. M. Moser and R. G. Spragg, St Louis, CV Mosby Co, 1982, 316 pp, $25.50.

Ambulatory Anesthesia Care, International Anesthesiology Clinics, Volume 20, Number 1, edited by S. W. Woo, Boston, Little, Brown and Co, 1982, 168 pp, $40.00/yr.

A Guide for Authors

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    The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119-25.

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Books and Other Monographs

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    Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

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7. Agency Publication

    National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

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II Nurses with a diploma or degree in nursing who are enrolled in nurse anesthesia schools;

III Students enrolled in programs leading to certification as Physician Assistants in Anesthesia/Anesthesiologist Assistants/Physician Associates in Anesthesiology; and

    Students enrolled in programs leading to certification as Respiratory Therapists or Technicians.

MEMBERSHIP TERMS AND COSTS: There are two membership periods available. The applicable membership dues must be paid in full with the application (i.e., annual payments of $15 will not be accepted.)

Two-Year Term—$35.00: Individuals applying for this period should have at least 18 months remaining in their training program at the time of application:

Three-Year Term—$52.00: Individuals applying for this period should have at least 30 months remaining in their training program at the time of application.

Note: The Educational Membership term should not extend more than six months following the ending of the training program covered. To that end, I.A.R.S. may, at its option, enter memberships retroactively to conform. In such instances, back issues of the Journal will be sent so that all 2-year memberships include 24 Journals, and all 3-year memberships include 36 Journals.

CANCELLATION OF MEMBERSHIP: Educational Membership can be cancelled upon written request to the IARS, and return of membership card, if the member is no longer enrolled in the training program. Pro-rated refunds will be made at the discretion of the I.A.R.S.

CONTINUATION OF MEMBERSHIP: After completion of the Educational Membership period, and upon payment of membership dues then in effect, individuals in Category I will be automatically continued as Members; and individuals in Categories II and III will be automatically continued as Associate Members of the I.A.R.S.

APPLICATION FORMS: The official application form (or facsimile thereof) must be used in applying for this membership, and payment must be submitted with the application. Application forms are available from the Cleveland business office, address above.

Safe and reliable.
Because he builds them
one at a time.

EVERY TWO SECONDS

FLUOTHANE® IS
(halothane, U.S.P.)

THE WORLDWIDE CHOICE.

Over 500 million administrations throughout the world. Well over 125 million administrations in the United States alone.

Somewhere in the world—every two seconds—someone makes another decision to use FLUOTHANE® (halothane, U.S.P.). And for good reasons:

□ FLUOTHANE has been more widely investigated than any other inhalation anesthetic.

□ The FLUOTHANE experience shows association with hepatotoxicity to be extremely rare.[1] According to conclusions drawn from the United States National Halothane Study and other studies,* unexplained jaundice following anesthesia with halothane "...was a rare occurrence (approximately 1:30,000 administrations) and...the overall safety record of the anesthetic was excellent."[2]

□ FLUOTHANE "...is nearest to the ideal [inhalation anesthetic] presently available for children of all ages."[3]

□ FLUOTHANE has been recommended as the "anesthetic of choice"[4] for asthmatics.

□ And, of particular benefit in geriatrics and cardiovascular surgery: Excessive respiratory depression is rarely a problem with FLUOTHANE. Nor does it produce an increase in salivary or bronchial secretions.

*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P. et al.: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

References:
1. Bunker, J.P., et al.: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology 43:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

the most widely used inhalation anesthetic in the world

FLUOTHANE®

(halothane, U.S.P.)

for a wide variety of techniques and procedures in patients of all ages

(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:

$$\begin{array}{ccc} F & & Br \\ | & & | \\ F-C-C-Cl \\ | & & | \\ F & & H \end{array}$$

The specific gravity is 1.872-1.877 at 20°C, and the boiling point (range) is 49°C – 51°C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20°C. The blood/gas coefficient is 2.5 at 37°C, and the olive oil/water coefficient is 220 at 37°C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), up to 0.00025% ammonia (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation.

FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is

possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

It has been reported that in genetically susceptible individuals, the use of general anesthetics and the muscle relaxant, succinylcholine, may trigger a syndrome known as malignant hyperthermic crisis. Monitoring temperature during surgery will aid in early recognition of this syndrome. Dantrolene sodium and supportive measures are generally indicated in the management of malignant hyperthermia.

Adverse Reactions. The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P., stabilized with 0.01% thymol (w/w), and up to 0.00025% ammonia (w/w).   **7197/R82**

For the response you want,
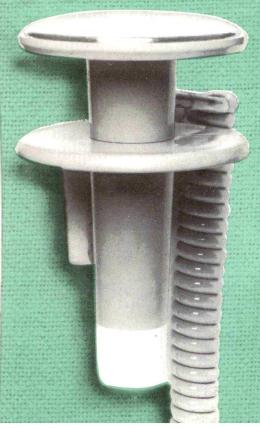
Pre-op

Injectable Valium (diazepam/Roche), administered intramuscularly approximately one hour before surgery, produces the antianxiety response you want. Patients, though calmer, typically remain well-oriented and able to cooperate. When an amnesic effect is desired, intravenous administration just prior to anesthesia produces diminished recall of unpleasant aspects of the induction period. (The dosage of concomitant narcotic analgesics should be reduced by at least one third and in some cases may be omitted.) Since it requires no reconstitution, Injectable Valium is ready immediately.
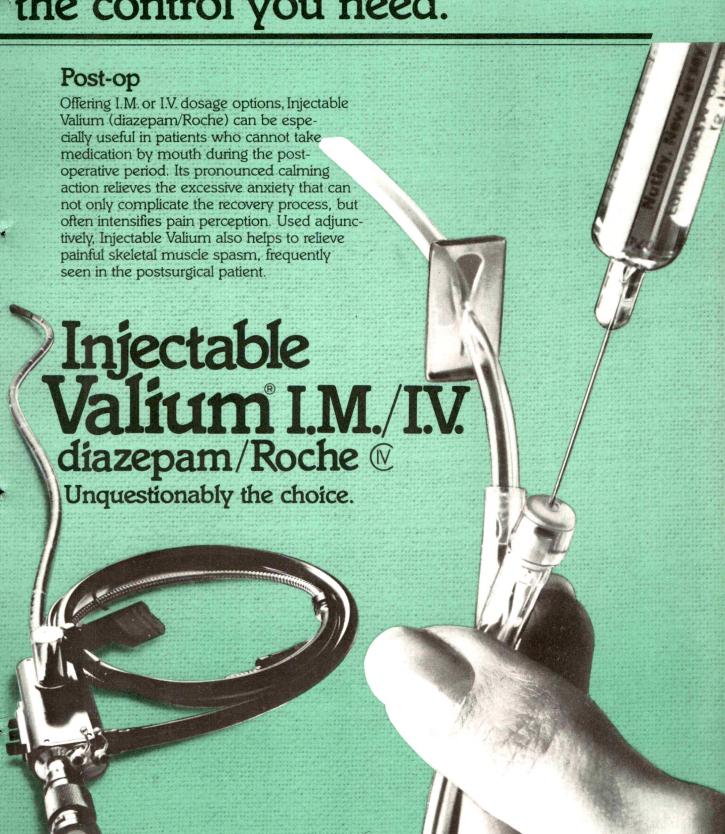
Pre-procedure

Excessive anxiety in patients facing such procedures as endoscopy or cardioversion can be relieved almost immediately by administering Injectable Valium (diazepam/Roche) I.V. Peak blood levels and expected clinical response are usually achieved in less than 3 minutes. Most patients are greatly relaxed, yet alert enough to respond to directions. And Valium provides the added advantage of predictable anterograde amnesia: usually lasting only 20 to 60 minutes, in sharp contrast to agents producing amnesia for up to 8 hours—sometimes longer. Used appropriately, Injectable Valium seldom significantly alters vital signs. It should be administered with caution to the elderly, the very ill and to patients with limited pulmonary reserve. Resuscitative facilities should be readily available.

the control you need.

Post-op

Offering I.M. or I.V. dosage options, Injectable Valium (diazepam/Roche) can be especially useful in patients who cannot take medication by mouth during the post-operative period. Its pronounced calming action relieves the excessive anxiety that can not only complicate the recovery process, but often intensifies pain perception. Used adjunctively, Injectable Valium also helps to relieve painful skeletal muscle spasm, frequently seen in the postsurgical patient.

Injectable Valium® I.M./I.V.
diazepam/Roche Ⓒ IV

Unquestionably the choice.

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Ready-to-use 2-ml Tel-E-Ject®
disposable syringes
2-ml ampuls, 10-ml vials } 5 mg/ml

versatile... and predictable

- prompt control of anxiety/apprehension
- anterograde amnesia of brief duration
- effective adjunctive skeletal muscle relaxant
- useful in outpatients as well as inpatients

Please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in. relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in paitents with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*
Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).
Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.
Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Not recommended for OB use.
Efficacy/safety not established in neonates (age 30 days or less), prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy. If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), i.e., phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis, phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice, periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)
For dosages in infants and children see below; have resuscitative facilities available.
I.M. use: by deep injection into the muscle.
I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.
Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, administer I.V. slowly; for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.
Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.
In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M., in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10, Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

⟨ROCHE⟩ Roche Laboratories
Division of Hoffmann-La Roche Inc.

Inapsine® (droperidol) Injection R

Before prescribing please consult complete prescribing information, of which the following is a brief summary.

DESCRIPTION:
2 ml. and 5 ml. ampoules
Each ml. contains:
Droperidol..2.5 mg.
Lactic acid for pH adjustment to 3.4 ± 0.4
10 ml. vials
Each ml. contains:
Droperidol..2.5 mg.
With 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY
Droperidol is a neuroleptic (tranquilizer) agent.

INDICATIONS: INAPSINE (droperidol) is indicated:
to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures;
for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia;
in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE* (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.
If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.
The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.
If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.
Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.
Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.
When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.
Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.*

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.
Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.
Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).
When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated respiratory arrest could occur. Elevated blood pressure, with or without preexisting hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved. Vital signs should be monitored routinely.
Usual Adult Dosage
I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.
II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
If INNOVAR* injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.
III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.
IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

HOW SUPPLIED: 2 ml. and 5 ml. ampoules-packages of 10; 10 ml. multiple-dose vials—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10
March 1980, Revised June 1980
*See full prescribing information for complete description.

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When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromid radical, a skin rash may be seen in an occasional patient. Such reactions usually subsid promptly upon discontinuance of the medication. Thrombophlebitis has been reporte subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously t reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1. mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to c simultaneous with its administration. Side effects, notably excessive secretions and bradycar dia are thereby minimized. Reversal dosages range from 0.1-0.25 mg /kg. Usually 10 or 20 m of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizin muscle relaxants. Although full recovery may occur within 15 minutes in most patients, other may require a half hour or more. Satisfactory reversal can be evident by adequate voluntar respiration, respiratory measurements and use of a peripheral nerve stimulator device. It i recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained recurarization has not been reported.

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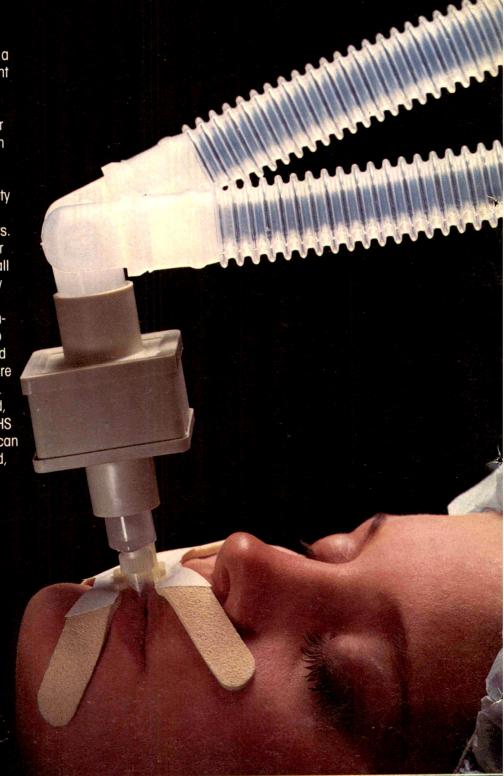
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Anesthesia and Analgesia

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Contents

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BOOK REVIEWS

When patients would rather not remember...

premedication with Ativan® (lorazepam) Injection IM or IV effectively reduces recall of events surrounding surgery

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Surgical procedures are perceived as frightening or unpleasant by most patients. If given the opportunity, many would rather not remember anything about the ordeal.

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ATIVAN® (LORAZEPAM) IV
INJECTION IM or IV

DESCRIPTION: Ativan* (lorazepam) Injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal failure. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately post-injection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure.* Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure.* EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP

HOW SUPPLIED: Ativan* (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.

For IM or IV injection.

Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

Wyeth Laboratories
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For one of medicine's most demanding skills... one of medicine's most dependable agents

Ethrane®

(enflurane)

precise control...stability of heart rhythm...
reduced relaxant requirement...prompt, smooth recovery
...organ toxicity rare or nonexistent

Ethrane
(enflurane) **10** years of experience confidence safety

Ohio Medical Anesthetics

For complete use information, please see following page.

Ethrane® (enflurane)

DESCRIPTION

ETHRANE (enflurane) (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether) (CHF2OCF2CHFCl) is a nonflammable inhalation anesthetic agent. The boiling point is 56.5°C at 760 mm Hg and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10}P = A + B/T$$

$$A = 7.967$$
$$B = -1678.4$$
$$T = °C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20°C is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C.

Enflurane is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary even in the presence of ultraviolet light. Enflurane is stable to strong base and does not decompose in contact with soda lime and does not react with aluminum, tin, brass, iron or copper. The partition coefficients of enflurane at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ETHRANE (enflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70 percent nitrous oxide—30 percent oxygen, and 1.17 in 30 percent nitrous oxide—70 percent oxygen.

Induction and recovery from anesthesia with enflurane are rapid. Enflurane has a mild, sweet odor. Enflurane may provide a mild stimulus to salivation or tracheobronchial secretions. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia can be changed rapidly by changing the inspired enflurane concentration. Enflurane reduces ventilation as depth of anesthesia increases. High PaCO2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. Enflurane provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during enflurane anesthesia. Enflurane anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with enflurane and injected with epinephrine containing solutions to achieve hemostasis in a highly vascular area (transsphenoidal surgery), it is recommended that 2 micrograms per kilogram (2 μg/kg) of epinephrine may be injected subcutaneously over a 10 minute period. This may be repeated up to 3 times per hour.

Example: Up to 10 ml of 1:100,000 epinephrine containing solution (10 μg/ml) may be injected subcutaneously over a 10 minute period in a 50 kilogram patient judged to have ordinary tolerance to epinephrine administration. No more than 30 ml of 1:100,000 epinephrine containing solution (10 μg/ml) should be administered to such a patient per hour. The concomitant administration of lidocaine enhances the safety of the use of epinephrine during enflurane anesthesia. This effect of lidocaine is dose related. All customary precautions in the use of vasoconstrictor substances should be observed.

Example Two: Alternatively, up to 20 ml of 1:200,000 epinephrine containing solution (5 μg/ml) may be substituted for 10 ml of 1:100,000 solution in the above example.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with enflurane. The NON-DEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of enflurane.

Biotransformation of enflurane in man results in low peak levels of serum fluoride averaging 15 μM/L. These levels are well below the 50 μM/L threshold level which can produce minimal renal damage in normal subjects. However, patients chronically ingesting isoniazid or other hydrazine containing compounds may metabolize greater amounts of enflurane. Although no significant renal dysfunction has been found thus far in such patients, peak serum fluoride levels can exceed 50 μM/L, particularly when anesthesia goes beyond 2 MAC hours. Depression of lymphocyte transformation does not follow prolonged enflurane anesthesia in man in the absence of surgery. Thus enflurane does not depress this aspect of the immune response.

Enflurane 0.25 to 1.0 percent (average 0.5 percent) provides analgesia equal to that produced by 30 to 60 percent (average 40 percent) nitrous oxide for vaginal delivery. With either agent, patients remain awake, cooperative, and oriented. Maternal blood losses are comparable. These clinical approaches produce normal Apgar scores. Serial neurobehavioral testing of the newborn during the first 24 hours of life reveals that neither enflurane nor nitrous oxide analgesia is associated with obvious neurobehavioral alterations. Neither enflurane nor nitrous oxide when used for obstetrical analgesia alters serum BUN, creatinine, uric acid or osmolality. The only difference in the use of these two agents for obstetrical analgesia appears to be higher inspired oxygen concentration that may be used with enflurane.

Analgesic doses of enflurane, up to approximately 1 percent, do not significantly depress the rate or force of uterine contraction during labor and delivery. A slowing of the rate of uterine contraction and a diminution of the force of uterine contraction is noted between the administration of 1 and 2 percent delivered enflurane; concentrations somewhere between 2 and 3 percent delivered enflurane may abolish uterine contractions. Enflurane displaces the myometrial response curve to oxytocin so that at lower concentrations of enflurane oxytocin will restore uterine contractions; however, as the dose of enflurane progresses (somewhere between 1.5 and 3 percent delivered enflurane) the response to oxytocin is diminished and then abolished. Uterine bleeding may be increased when enflurane is used in higher concentrations for vaginal delivery or to facilitate delivery by Cesarean section, however, this has not been demonstrated within the recommended dosage range (see DOSAGE AND ADMINISTRATION section). Mean estimated blood loss in patients anesthetized for therapeutic abortion with 1 percent enflurane in 70 percent nitrous oxide with oxygen is approximately twice that noted following therapeutic abortion performed with the use of a local anesthetic technique (40 ml versus 20 ml).

INDICATIONS AND USAGE

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Enflurane may be used to provide analgesia for vaginal delivery. Low concentrations of enflurane (see DOSAGE AND ADMINISTRATION) may also be used to supplement other general anesthetic agents during delivery by Cesarean section. Higher concentrations of enflurane may produce uterine relaxation and an increase in uterine bleeding.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS)
Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics
Known or suspected genetic susceptibility to malignant hyperthermia

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentrations usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged enflurane anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to depth of anesthesia. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

PRECAUTIONS

The action of nondepolarizing relaxants is augmented by ETHRANE (enflurane). Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from neuromuscular blockade will be longer in the presence of enflurane than when halothane or nitrous oxide with a balanced technique are used.

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. Enflurane should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug.

In susceptible individuals, enflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc. The syndrome of malignant hyperthermia secondary to enflurane appears to be rare; by March 1980, 35 cases had been reported in North America for an approximate incidence of 1/725,000 enflurane anesthetics.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly, early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO2 absorption system (hot canister). PaO2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., enflurane), administration of intravenous dantrolene, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. Renal failure may appear later, and urine flow should be sustained if possible.

Swiss ICR mice were given enflurane to determine whether such exposure might induce neoplasia. Enflurane was given at ½, ¼, and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice who were given the same background gases, but not the anesthetic.

Exposure of mice to 20 hours of 1.2 percent enflurane causes a small (about ½ of 1%) but statistically significant increase in sperm abnormalities. In contrast to these results, in vitro approaches to the study of mutagenesis (Ames test, sister chromatid exchange test, and the 8-azaguanidine system) have not shown a mutagenic effect of enflurane.

Pregnancy Category B:
Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to enflurane. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

ADVERSE REACTIONS

1. Malignant hyperthermia
2. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia
3. Hypotension and respiratory depression have been reported
4. Arrhythmias, shivering, nausea, and vomiting have been reported
5. Elevation of the white blood count has been observed

OVERDOSAGE

In the event of overdosage, the following action should be taken:
Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:
  a) vaporizers calibrated specifically for enflurane;
  b) vaporizers from which delivered flows can easily and readily be calculated

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by enflurane and that enflurane does not alter heart rate. The use of anticholinergic drugs is a matter of choice.

Surgical Anesthesia: Induction may be achieved using enflurane alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the enflurane mixture. In general, inspired concentrations of 2.0-4.5 percent enflurane produce surgical anesthesia in 7-10 minutes.

Surgical levels of anesthesia may be maintained with 0.5-3 percent enflurane. Maintenance concentrations should not exceed 3 percent. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of enflurane concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Analgesia: Enflurane 0.25 to 1.0 percent provides analgesia equal to that produced by 30 to 60 percent nitrous oxide. These concentrations normally do not produce amnesia. See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section.

Cesarean Section: Enflurane should ordinarily be administered in the concentration range of 0.5 to 1.0 percent to supplement other general anesthetics. See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section.

HOW SUPPLIED

ETHRANE (enflurane) is packaged in 125 and 250 ml amber-colored bottles.

Ethrane (enflurane) **10** years of experience confidence safety

Ohio Medical Anesthetics

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PHARMACEUTICA

Introducing a new anesthetic technique:

This new technique—pre-intubation analgesic loading—involves administering enough SUBLIMAZE® (fentanyl) prior to intubation to last generally the length of the procedure. Pre-intubation upfront loading employs the pharmacokinetic properties of SUBLIMAZE® (fentanyl) to best advantage compared with p.r.n. use or administration of the drug incrementally throughout the procedure.

For further information and general guidelines on pre-intubation analgesic loading with SUBLIMAZE® (fentanyl), please contact your Janssen representative or write Janssen Pharmaceutica.

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Sublimaze®
(fentanyl) Injection C

Protect from light. Store at room temperature.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

DESCRIPTION
Each ml. contains:
Fentanyl . . . . 50 mcg. (0.05 mg.) as the citrate
Warning: May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0-7.5.

CONTRAINDICATIONS
SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS
AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATION EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA. See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition. Where moderate or high doses are used (above 10 mcg./kg.), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received SUBLIMAZE (fentanyl). It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Drug Dependence—SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure—SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children—The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy—The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS
The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of SUBLIMAZE (fentanyl) are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol) hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol).

When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS
As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with *INAPSINE* (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION
50 mcg. = .05 mg. = 1 ml.

Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

I. *Premedication*—Premedication (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered *intramuscularly* 30 to 60 minutes prior to surgery.

II. *Adjunct to General Anesthesia*—See Dosage Range Chart

III. *Adjunct to Regional Anesthesia*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

IV. *Postoperatively (recovery room)*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usual Children's Dosage: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 20 to 30 mcg. (0.02 to 0.03 mg.)(0.4 to 0.6 ml.) per 20 to 25 pounds is recommended.

DOSAGE RANGE CHART

TOTAL DOSAGE

Low dose—2 mcg./kg. (.002 mg./kg.) (.04 ml./kg.) SUBLIMAZE® injection. Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period. *Maintenance:* Additional dosages of SUBLIMAZE® injection are infrequently needed in these minor procedures.

Moderate dose—2-20 mcg./kg. (.002-.02 mg./kg.)(.04-0.4 ml./kg.) SUBLIMAZE® injection. Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential. *Maintenance:* 25 to 100 mcg. (0.025 to 0.1 mg.)(0.5 to 2.0 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

High dose—20-50 mcg./kg. (.02-.05 mg./kg.)(0.4-1 ml./kg.) SUBLIMAZE® injection. During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20-50 mcg./kg. (.02-.05 mg.)(0.4-1 ml.) of SUBLIMAZE® injection with nitrous oxide oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH, and prolactin.

When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression.

The main objective of this technique would be to produce "stress free" anesthesia. *Maintenance:* Maintenance dosage (ranging from 25 mcg. (.025 mg.)(0.5 ml.) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

As a General Anesthetic
When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg./kg. (.05 to 0.1 mg./kg.)(1 to 2 ml./kg.) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg./kg. (.15 mg./kg.)(3 ml./kg.) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

OVERDOSAGE
Manifestations: The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; and oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

HOW SUPPLIED
2 ml. and 5 ml. ampoules—packages of 10.
NDC 50458-030-02 **NDC** 50458-030-05

10 ml. and 20 ml. ampoules—packages of 5.
NDC 50458-030-10 **NDC** 50458-030-20
(For intravenous use by hospital personnel specifically trained in the use of narcotic analgesics).

March, 1980. Revised June, 1980. January, 1981
U.S. Patent No. 3, 164 600

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Janssen Pharmaceutica Inc., 501 George St., New Brunswick, N.J. 08903

JPI-255

The first of a new generation of Critical Care Monitors.

Monitoring tcPO₂ is only the beginning.

The new Critikon Transcutaneous Monitor is the first of a series of technologically advanced critical care monitors with features such as the Interactive Display Panel that provides simplified operation through 2-way communication between you and the monitor.

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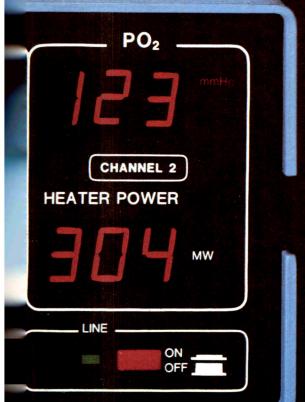
800-237-7541
(FL: 800-282-9151).

Please see next page for brief summary.

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BRIEF SUMMARY:

ADDRESS CHANGE NOTICE

(16)

KIT

A sterile, disposable, prefilled syringe and cannula kit for convenient laryngotracheal anesthesia prior to intubation, diagnosis, surgery.

25% more drug than other kits*
* contains 5ml Xylocaine* (lidocaine HCl) 4% Solution to allow for greater range of dosage determination

Calibrated barrel
* marked in 1/2 ml increments to aid in proper dose determination and accuracy of drug delivery

Prefilled syringe
* totally sterile and self-contained
* no vial to insert, no risk of contamination

Hub guard
* a simple twist quickly activates the syringe and readies the unit for attachment of cannula or needle

Luer hub
* firmly secures needle or cannula

Safety strap
* an extra precaution against inadvertent cannula disengagement

Separate syringe unit
* lets you choose either intraoral or transtracheal routes of administration at your discretion

Cannula
* anatomically curved to facilitate introduction into larynx and trachea.
* easily attaches to syringe, virtually no assembly time

*Although absorption of lidocaine from respiratory mucosa varies widely among individuals, blood concentrations achieved by this route can rise to levels comparable to those reached by similar doses infused intravenously, and in some cases almost as rapidly.[1,2,3]

REFERENCES
1. Bromage P: Concentrations of lidocaine in the blood after intravenous and endotracheal administration. Anaesthesia, 16:461, 1961.
2. Chu S: Plasma concentration of lidocaine after endotracheal spray. Anesth. Analg., 54:438, 1975.
3. Pelton D: Plasma lidocaine concentrations following topical aerosol application to the trachea and bronchi. Canad. Anaesth. Soc. J., 17:250, 1970.

ASTRA® | **Astra Pharmaceutical Products, Inc.**
Worcester, Massachusetts 01606

(Please see following page for a brief summary of prescribing information.)

AST-1247

Xylocaine®
(lidocaine hydrochloride)
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❚

Inapsine® (droperidol) Injection ℞

Before prescribing please consult complete prescribing information, of which the following is a brief summary.

DESCRIPTION:
2 ml. and 5 ml. ampoules
Each ml. contains:
Droperidol .... 2.5 mg.
Lactic acid for pH adjustment to 3.4 ± 0.4
10 ml. vials
Each ml. contains:
Droperidol .... 2.5 mg.
With 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY
Droperidol is a neuroleptic (tranquilizer) agent.

INDICATIONS: INAPSINE (droperidol) is indicated:
to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures;
for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia;
in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE* (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.
If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.
The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.
If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.
Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.
Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.
When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.
Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.*

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.
Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.
Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).
When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated respiratory arrest could occur. Elevated blood pressure, with or without preexisting hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved. Vital signs should be monitored routinely.
Usual Adult Dosage
I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.
II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
If INNOVAR* injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.
III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.
IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

HOW SUPPLIED: 2 ml. and 5 ml. ampoules-packages of 10; 10 ml. multiple-dose vials—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10

March 1980, Revised June 1980
*See full prescribing information for complete description.

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Janssen Pharmaceutica Inc, 501 George St., New Brunswick, N.J. 08903

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LOWER
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BELOW PEEP

UPPER
PRESS. LIMIT

○ LOW RATE
0-4-4

○ HIGH RATE
4-40

INFANTS
0-4 l/min

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0-40 l/min

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For an uneventful anesthesia course

In preop, you'll appreciate the good sedative effect of Stadol and reduction in patient apprehension.

Intraoperatively, Stadol provides smooth induction and emergence. The return to spontaneous respiration is rapid, so naloxone is rarely required.

In the recovery room, dosage can be repeated or increased, if necessary, to provide full pain relief with little fear of causing respiratory depression greater than that produced by 10 mg morphine.

Rebound respiratory depression, as sometimes seen in recovery after fentanyl, does not occur. Hypotensive effects are limited. Nausea or vomiting is rare.

Stadol is adaptable to a wide range of procedures, is compatible with your routines and is nonscheduled so you can keep it conveniently on your anesthesia cart.

Note: Stadol should not be administered to patients who have significant recent narcotic experience; its narcotic antagonist properties may induce withdrawal reactions unless detoxification is accomplished prior to use.

Stadol® IM IV

(butorphanol tartrate)

for moderate to severe pain… the hospital-proven analgesic with the safety difference

Stadol IM IV
(butorphanol tartrate)

the effective analgesic with the safety difference

Brief Summary of Prescribing Information
STADOL® (butorphanol tartrate)

For complete information, consult Official Package Circular.

(2) 12/10/79

INDICATIONS AND USAGE—Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS—Patients Physically Dependent on Narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.
Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Drug Dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects: Because Stadol increases the work of the heart, especially the pulmonary circuit, the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS—Certain Respiratory Conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Preoperative or Preanesthetic Medication: Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Balanced Anesthesia: The use of pancuronium in combination with Stadol may cause an increase in conjunctival changes.

Usage in Pregnancy: The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.
Reproduction studies have been performed in rats, mice and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in Labor and Delivery: Safety to the mother and fetus following administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers: The use of Stadol in lactating mothers who are nursing their infants is not recommended since it is not known whether this drug is excreted in human milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children: Safety and efficacy in children below age 18 years have not been established.

ADVERSE REACTIONS—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%). Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%). Other adverse reactions which may occur (reported incidence of less than 1%) are:
CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations
Autonomic: flushing and warmth, dry mouth, sensitivity to cold
Cardiovascular: palpitation, increase or decrease of blood pressure
Gastrointestinal: vomiting
Respiratory: slowing of respiration, shallow breathing
Dermatological: rash or hives
Eye: diplopia or blurred vision

OVERDOSAGE—Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

HOW SUPPLIED—Stadol (butorphanol tartrate) Injection for I.M. or I.V. use, is available as follows:

NDC 0015-5644-20—2 mg per ml, 2-ml vial
NDC 0015-5645-20—1 mg per ml, 1-ml vial
NDC 0015-5646-20—2 mg per ml, 1-ml vial
NDC 0015-5646-23—2 mg per ml, 1-ml Disposable Syringe
NDC 0015-5648-20—2 mg per ml, 10-ml multi-dose vial

Marcaine® HCl
(bupivacaine HCl injection, USP)
with or without epinephrine 1:200,000

Please consult full prescribing information before prescribing. A summary follows:
Indications. Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.
Contraindication. Marcaine is contraindicated in patients with known hypersensitivity to it.
Warnings. RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.
Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.
The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).
Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.
Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.
Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions. The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.
The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.
Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.
Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.
Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.
Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Use in Ophthalmic Surgery. When Marcaine 0.75% is used for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Therefore, presence of akinesia rather than anesthesia alone should determine readiness of the patient for surgery.

Adverse Reactions. Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.
Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings). *Allergic reactions,* which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value. Sensitivity to methylparaben preservatives added to multiple dose vials has been reported. Single dose vials without methylparaben are also available.
Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.
Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

Composition of Solutions.
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Marcaine 0.5% — Each ml contains 5 mg bupivacaine with NaCl for isotonicity in water for injection.
Marcaine 0.75% — Each ml contains 7.5 mg bupivacaine with NaCl for isotonicity in water for injection.
In multiple dose vials, each ml also contains 1 mg methylparaben.
In epinephrine, each ml also contains 0.0091 mg epinephrine bitartrate, 0.5 mg sodium bisulfite, 0.001 ml monothioglycerol, 2 mg ascorbic acid, 0.0017 ml 60% sodium lactate, and 0.1 mg edetate calcium disodium.

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The Minimum Alveolar Concentration of Nitrous Oxide in Man

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Graham Smith, BSc, FFARCS,§ Dana Wetstone, MD,‖ and Kent H. Smith, DVM, PhD¶

The potency and anesthetic state produced by nitrous oxide alone were investigated in order to clarify its contribution to the effect of other anesthetic agents. Seven volunteers anesthetized with 1.55 atm absolute N_2O in a pressure chamber displayed muscle rigidity with jerking movements, labored and rapid breathing, sweating, and dilated pupils. At 1.1 atm absolute N_2O, relaxation and quiescence occurred, sweating ceased, and pupil size decreased. Determination of MAC (using tetanic electrical impulses as the noxious stimulus) produced a mean value of 1.04 ± 0.10 (SE) atm absolute. All subjects complained of nausea and vomiting after anesthesia.

Key Words: ANESTHETICS, Gases: nitrous oxide; POTENCY, Anesthetics: MAC.

THE CONCENTRATION of nitrous oxide necessary to produce anesthesia far exceeds that required for potent inhaled agents commonly used today. Indeed, using N_2O, Horace Wells failed in the first public attempt to demonstrate anesthesia (1). Although investigators later found that high concentrations of N_2O kept some patients immobile for minor procedures, such immobility may have resulted in part from a deficit of oxygen. However, Paul Bert (2) established that N_2O could provide anesthesia in a pressure chamber without producing an associated

blueness of the lips. Under these conditions, surgery could proceed when the concentration of nitrous oxide approximated 1 atm.

Surgery in pressure chambers never became popular, and the effective use of N_2O today requires its combination with other depressants. N_2O seems to lessen substantially the requirement for concomitantly administered agents and to do so in an additive fashion (3–6). Extrapolating these data to greater N_2O contributions shows that the MAC for N_2O in man approximates 1 atm. This value agrees with Bert's estimation, and with the prediction of the potency of N_2O based on its oil/gas partition coefficient (3–12).

A more precise determination of the potency of N_2O when used alone would provide a clearer understanding of its contribution to the effect of other agents. As Bert (2) noted, such studies require the use of hyperbaric pressures to ensure adequate oxygenation. An opportunity to measure the anesthetic potency (MAC) of N_2O in man arose during studies that investigated its cardiorespiratory effects at high pressures. In this paper, we describe the potency and anesthetic state produced by N_2O alone.

Methods

We studied seven healthy, young (21 to 35 years old) male volunteers, who all gave written consent. Any applicant who had used psychotropic drugs did not participate.

The subjects fasted for at least 8 hours before the study. Insertion of arterial, peripheral, and central venous cannulas permitted awake (control) measurements of cardiorespiratory variables while the subjects breathed air at ambient pressure (1 atm absolute, P_{IO_2} = 149) and at 1.87 atm absolute. Preparation and the obtaining of control measurements took 2 to 4 hours.

N_2O (82%) provided a rapid induction of anesthesia at a chamber pressure of 1.87 atm absolute. An IBC polarographic oxygen electrode or a Beckman E2 oxygen analyzer (placed outside the chamber) measured P_{IO_2} (dry) at 1 atm absolute. The concomitant measurements obtained from both instruments agreed closely. When available (in four of seven subjects), we accepted the E2 measurement as the best indicator of P_{IO_2}. Succinylcholine (80 mg IV) and topical spray of the larynx with 4% lidocaine facilitated endotracheal intubation. Over the next 2½ to 3 hours, we studied the cardiorespiratory effects of N_2O (including the response to a carbon dioxide challenge) at partial pressures of N_2O ranging from 1.1 to 1.55 atm absolute (results to appear in a separate report). The determination of MAC followed these measurements.

The noxious stimulus consisted of a tetanic electrical stimulation (100-Hz square-wave pulse of 0.1-msec duration at 80 to 110 V) applied for 10 seconds through needle electrodes placed close to the ulnar nerves at both wrists separately and then (in six of seven subjects) concomitantly. We first applied this stimulus at approximately 1.1 atm absolute N_2O. If movement (of head or unstimulated extremities) did not occur, we decreased the nitrous oxide partial pressure in 0.2-atm absolute steps every 15 minutes until unilateral or bilateral stimulation elicited movement. If movement occurred, we increased the partial pressure by 0.2 atm absolute, and so forth. The process continued until we obtained at least three bracketings (i.e., nonmovement, movement, nonmovement; or movement, nonmovement, movement).

The relationship

$$P_{IN_2O} = (1 - P_{IO_2}/PB) (PB - P_{H_2O})$$

allowed calculation of the wet inspired N_2O partial pressure for each level where P_{IO_2} = dry inspired oxygen partial pressure; PB = 760 times chamber pressure in atmospheres absolute; and P_{H_2O} = 47 torr (we maintained each subject's temperature at 37°C). We converted the wet inspired N_2O partial pressure to an alveolar partial pressure (approximately a 5-torr increase) using the alveolar gas equation and assum-

ing a respiratory quotient of 0.8 and a Pa_{CO_2} of 40 torr. The average of the bracketing alveolar values thus obtained produced the MAC values for each subject.

Results

In most subjects, 1.55 atm absolute nitrous oxide produced rigidity of abdominal muscles and, frequently, catatonic jerking of extremities. One subject became opisthotonic. Tachypnea (47.4 ± 2.5 breaths/min) accompanied labored breathing, and sweating often occurred. Dilated pupils and, occasionally, open eyes gave an impression of wakefulness, yet no subject responded to verbal commands (or electrical stimulation). A few subjects exhibited cycles of this type of hyperactivity that alternated with moments of apparent relaxation, each cycle lasting several minutes.

At 1.1 atm absolute N_2O, all subjects relaxed, the spontaneous jerking movements of the limbs vanished, sweating ceased, the eyes closed, and pupil size decreased. The tachypnea decreased (30.0 ± 1.5 breaths/min). Indeed, the subjects seemed to go to sleep, manifesting a state appropriate for surgery. All subjects complained of postanesthetic nausea and vomiting.

For six subjects, we found the following individual MAC values: 0.78, 0.80, 0.97, 0.99, 1.29, and 1.40 atm absolute, mean MAC of 1.04 ± 0.10 (SE) atm absolute. In one additional subject we assessed the effect of only two levels of N_2O without finding a bracketing value for MAC. Because of the incompleteness of the data for this subject, we elected not to include them in the analysis of MAC. The lowest alveolar N_2O value at which we tested this subject equaled 0.9 atm absolute (no movement).

Discussion

The deletion of the incomplete data for one of our subjects increased our value for MAC; inclusion of the lowest value for this subject produces a MAC of 1.00 ± 0.09 atm absolute. On the other hand, our value of 1.04 atm absolute may underestimate the true MAC for two reasons. First, the studies on MAC followed other studies that used higher partial pressures of N_2O for several hours. Thus, the true alveolar partial pressure of N_2O may have exceeded our estimates of it because of continuing elimination of N_2O. Second, the work of Saidman and Eger (3) suggests that electrical stimulation may not quite provide a supramaximal stimulus. The somewhat wider range of MAC values we found (60% of the MAC value)

% of MAC of second anesthetic
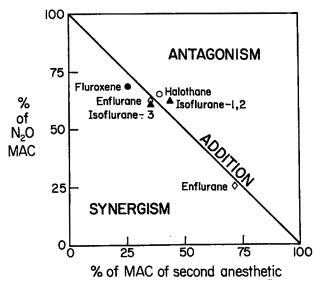
FIGURE. Combination of N_2O and a potent inhaled anesthetic decreases partial pressure requirement for each. Report contains data sources for such pairs. Percentage of MAC that each agent must contribute to produce immobility (as a combination) in 50% of patients (i.e., 100 times partial pressure required/ MAC) has been calculated. To obtain alveolar values for N_2O from reported inspired values (usually obtained by measuring O_2 and assuming that N_2O comprised the difference), percentage of concomitantly administered potent agent was subtracted and multiplied by 0.938 (to correct for dilution by water vapor). It was assumed that effects of respiratory quotient and continuing N_2O uptake offset each other, and therefore no correction for these factors was made. "Isoflurane-1,2" refers to two younger age groups studied by Stevens et al (6), whereas "isoflurane-3" refers to results from patients aged 55 years or older. Diagonal line labeled "addition" indicates where data points would fall in combination of N_2O with indicated potent agent produced simply an additive effect.

also may indicate a less than supramaximal stimulus. However, the similarity of values obtained from bilateral vs unilateral stimulation imply that stimulation approached a supramaximal level.

The results of several previous studies (3–6, 10) indirectly support the accuracy of our MAC value for N_2O. Using those results and the present data, we constructed an isobologram demonstrating that the concomitant use of N_2O with other inhaled anesthetics appears to produce an additive effect (Figure). As other studies in humans also have shown additivity between mixtures of two inhaled agents (7, 8), these results suggest that our MAC value for nitrous oxide reasonably approximates the true value. The MAC value of 1.04 atm absolute and the evidence that N_2O simply adds to the effect of other inhaled anesthetics, means that 1% N_2O equals slightly less than 1% of the MAC of other agents.

Similarly, an examination of the correlation between lipid solubility and potency supports our value.

In middle-aged humans, MAC (in atmospheres) times the oil/gas partition coefficient for several inhaled agents equals 1.34 ± 0.10 (3–12). The product of our value for N_2O MAC and an oil/gas partition coefficient of 1.4 (11) equals 1.46. This slightly higher product for N_2O may have resulted from the youthfulness of our subjects. Younger patients have higher MAC values for isoflurane (6) and halothane (13). They also might have a higher N_2O MAC than the middle-aged patients whose MAC values produced the 1.34 figure. Nevertheless, the 1.46 value for N_2O falls well within the range of values found with other agents.

The consistent occurrence of postanesthetic nausea and vomiting may indicate that N_2O provokes an increase in sympathetic activity, as a high incidence of these complications also follows anesthesia with other agents that do increase such activity (cyclopropane, ether, fluroxene). The dilated pupils of our subjects similarly suggest an increase in sympathetic activity. Also, the addition of nitrous oxide to an agent such as halothane causes serum concentrations of norepinephrine to increase (14).

Seevers and Waters (15) stated that: "Were it a more potent gas, nitrous oxide would qualify as the ideal anesthetic." And Gwathmey (16) wrote: "Nitrous oxide and oxygen gas is unquestionably the safest anesthetic in the world; anybody studying the subject clinically and theoretically knows that." Our work may suggest another view. At 1.5 MAC, N_2O produced rigidity, jerking movements, diaphoresis, dilated pupils, and labored breathing and tachypnea. Muscle rigidity precluded endoscopy (hence the use of succinylcholine to facilitate endotracheal intubation), and nausea and vomiting occurred following anesthesia in all cases. At anesthetizing partial pressures, N_2O displayed less than "ideal" properties. We wonder what effect yet higher concentrations might have had: better anesthesia or greater hyperreactivity?

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Effects of Positive End-Expiratory Pressure on Carotid Blood Flow during Closed-Chest Cardiopulmonary Resuscitation in Dogs

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Ido, Y., Goto, H., Lavin, M. J., Robinson, J. D., Mangold, J. V., and Arakawa, K.: Effects of positive end-expiratory pressure on carotid blood flow during closed-chest cardiopulmonary resuscitation. Anesth Analg 1982;61:557-60.

The effect of continuous increases in intrathoracic pressure by positive end-expiratory pressure (PEEP) on common carotid artery blood flow (CCABF) and arterial blood gas tensions and pH during standard closed-chest cardiopulmonary resuscitation was studied in dogs. CCABF was measured at various levels of PEEP by means of the bubble flowmeter in hypervolemic, normovolemic, and hypovolemic dogs. PEEP was increased and then decreased in 5-cm H_2O increments with the highest level being 20 cm H_2O. Arterial blood samples were obtained approximately 15 minutes before ventricular fibrillation was induced with a transthoracic electric shock during zero end-expiratory pressure during increases in PEEP to 20 cm H_2O, and again during decreases to zero end-expiratory pressure. CCABF increased stepwise with increasing levels of PEEP in hypervolemic dogs, whereas it decreased stepwise with increasing levels of PEEP in hypovolemic dogs. In normovolemic dogs, CCABF increased only when the PEEP was 5 cm H_2O. Severe metabolic acidosis developed in both hypovolemic and normovolemic dogs at the end of 18 minutes of cardiopulmonary resuscitation. It is speculated that PEEP can either increase CCABF by increasing intrathoracic pressure during chest compression or decrease the CCABF by decreasing venous return during chest compressions, depending on the circulating blood volume. Data suggest that even low levels of PEEP are contraindicated in hypovolemia. Although changes in cerebral perfusion caused by PEEP were not investigated, it is suggested that some degree of PEEP may be beneficial in the hypervolemic state during cardiopulmonary resuscitation.

Key Words: VENTILATION: continuous positive pressure; positive end-expiratory pressure.

AFTER Kouwenhoven et al (1) first introduced external cardiac massage, it was generally assumed that blood flow during cardiopulmonary resuscitation (CPR) results from direct compression of the heart between the sternum and vertebral column. In 1980, Rudikoff and colleagues (2) postulated a new theory, the so-called thoracic pump mechanism. According to this theory, fluctuations of intrathoracic pressure are more responsible for forward blood flow during CPR than direct cardiac compression. This may explain several clinical situations, such as cough CPR (3) or successful CPR in emphysematous patients

in whom direct cardiac compression may be ineffective because of a markedly increased anteroposterior chest diameter. Chandra and colleagues (4) introduced a new concept of CPR based on their observation that carotid blood flow was augmented by the increase in intrathoracic pressure that occurred with simultaneous ventilation and chest compression. We were interested in investigating the effect in dogs of continuous increase in intrathoracic pressure achieved by various levels of positive end-expiratory pressure (PEEP) on common carotid artery blood flow (CCABF) and arterial blood gas tensions and pH during standard CPR.

Methods

Eighteen mongrel dogs, weighing 18 to 24 kg each, were anesthetized with intravenous sodium pentobarbital (25 mg/kg of body weight). Following tracheal intubation, the dogs were paralyzed with 0.1 mg/kg of pancuronium bromide and mechanically ventilated

by an Ohio anesthesia ventrilator with 100% oxygen using a tidal volume of 15 ml/kg. The respiratory rate was adjusted to achieve the arterial carbon dioxide tensions desired. Anesthesia was maintained with intermittent intravenous administration of ketamine hydrochloride. The left femoral artery was cannulated to monitor arterial blood pressure and obtain blood samples. Central venous pressure was monitored via a catheter inserted into the thoracic vena cava through the femoral vein and its proper position confirmed by observing fluctuation of pressure during intermittent positive-pressure ventilation. All pressure measurements, including airway pressure, were continuously monitored and recorded with a Hewlett-Packard 7758 eight-channel recording system and 1290-A quartz transducers, along with lead II electrocardiogram (ECG) recording. Rectal temperature was monitored with a Yellow Springs thermometer and was held at $37 \pm 1°C$.

The right common carotid artery was exposed and a shunt was placed (after administration of 4 mg/kg of heparin) to measure carotid blood flow by the bubble flowmeter method (5). An electromagnetic flowmeter was not used as it had proven to be overly sensitive to mechanical motion, resulting in artifacts during CPR (6).

Before induced ventricular fibrillation, acid-base balance was rechecked and corrected to within normal limits by adjustment of respiratory rate and by administration of sodium bicarbonate. Dogs were divided into three groups: (a) normovolemic [central venous pressure (CVP) 5 to 10 cm H_2O], (b) hypervolemic (CVP > 15 cm H_2O), and (c) hypovolemic (CVP < 2 cm H_2O). The CVP of the normovolemic group was adjusted by crystalloid infusion as needed. Hypervolemia was produced by the transfusion of 20 to 25 ml/kg of blood as well as by crystalloid infusion. The dogs with low CVP readings served as the hypovolemic group and their CVPs were further decreased by 15 ml/kg of phlebotomy. When the CVP reached the desired level, ventricular fibrillation was induced with a 2-second 110-Volt ac transthoracic electric shock. Circulatory arrest was allowed to persist for 1 minute before standard closed-chest CPR was instituted. External chest compression was performed with the chest Thumper mechanical resuscitator (Michigan Instruments, Inc., Grand Rapids, MI) at the rate of 68 compressions per minute. After every fifth chest compression without a pause, the ventilator was triggered manually with a tidal volume of 15 ml/kg. After 2 minutes of standard closed-chest CPR at zero end-expiratory pressure (ZEEP), PEEP was pro-

duced by directing exhalation through a column of water. PEEP was increased stepwise by 5 to 20 cm H_2O and decreased stepwise to ZEEP for a period of 2 minutes for each degree of PEEP. CCABF was measured twice, if possible, and averaged for each level of PEEP and ZEEP. Arterial blood was sampled for measurement of gas tensions and pH during the first and last ZEEP and when PEEP was 20 cm H_2O. All values of CCABF were compared with the control value during initial ZEEP and were analyzed by Student's t-test with $p < 0.05$ being regarded as statistically significant.

Results

Mean CCABF at first ZEEP was 7.5 ± 1.2 (SE) ml/min, 23.4 ± 2.8 ml/min, and 4.0 ± 1.1 ml/min for normovolemic, hypervolemic, and hypovolemic dogs, respectively. Changes in CCABF associated with PEEP are shown in the Figure. The mean values of CCABF during the first ZEEP, which were used as a control, were normalized to a dimensionless 100 to make comparison easier among the three groups. In normovolemic dogs, CCABF decreased with increasing PEEP after a significant increase at the initial 5 cm H_2O PEEP. CCABF increased stepwise with increasing PEEP in hypervolemic dogs, reaching 164% of control values at 20 cm H_2O PEEP and returning at the last ZEEP to less than the base line value (94%). In contrast, CCABF in hypovolemic dogs was decreased
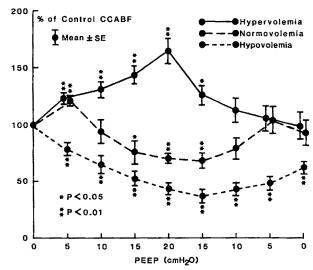
FIGURE. Common carotid arterial blood flow (CCABF) during cardiopulmonary resuscitation (CPR) at various levels of positive end-expiratory pressure (PEEP) in hypervolemic, normovolemic, and hypovolemic dogs. Mean control values of CCABF at first zero PEEP are normalized to a dimensionless 100; their standard errors are omitted here.

stepwise by PEEP, with the lowest (37%) CCABF obtained when PEEP was 15 cm H_2O; CCABF was only 62% of control values when the PEEP was subsequently decreased to ZEEP.

Blood gas tensions and acid-base changes in normovolemic, hypervolemic, and hypovolemic dogs, respectively, are summarized in Tables 1 to 3. Pa_{O_2} decreased significantly from preventricular fibrillation levels during the first ZEEP in all three groups. During CPR, Pa_{O_2} did not decrease further but instead increased toward the preventricular fibrillation Pa_{O_2} values at 20 cm H_2O PEEP, particularly in hypervolemic dogs. All three groups of dogs were significantly hyperventilated during CPR. There was progressive development of metabolic acidosis in normovolemic and hypovolemic dogs in the course of 18 minutes of CPR. Hypervolemic dogs developed significant alkalosis at 20 cm H_2O PEEP and the last ZEEP.

Discussion

It is well known that PEEP can improve blood oxygenation, but at the same time it may decrease cardiac output because of the reduction in venous return (7). According to the new concepts of CPR, increasing generalized intrathoracic pressure increases forward blood flow. Therefore, the increased intrathoracic pressure caused by PEEP during CPR may have two discrepant effects on forward blood flow: (a) decreasing forward blood flow by decreasing venous return between compressions, and (b) increasing forward blood flow by increased driving pressure during chest compression.

We applied each level of PEEP for a period of only 2 minutes as Hodgkin et al (8) did in their study. In addition, in our study PEEP was increased and then decreased stepwise over 18 minutes of CPR. Thus, it

TABLE 1

Normovolemic Group (n = 6)*

	Pre-VF	First ZEEP	20 cm H_2O PEEP	Last ZEEP
pH	7.39 ± 0.01	7.40 ± 0.02	7.43 ± 0.05	7.34 ± 0.03
Pa_{O_2} (mm Hg)	428 ± 42.7	299 ± 44.4‡	303 ± 46.8†	293 ± 29.8‡
Pa_{CO_2} (mm Hg)	39 ± 0.9	29 ± 3.1†	25 ± 3.6†	26 ± 3.3†
Base excess (meq/L)	−1.2 ± 0.7	−5.0 ± 2.3	−5.6 ± 2.3	−10.5 ± 1.8‡

* Values are means ± SE. Abbreviations used are: Pre-VF, preventricular fibrillation; ZEEP, zero end-expiratory pressure; PEEP, positive end-expiratory pressure.
† Significant difference ($p < 0.05$) from Pre-VF value.
‡ Significant difference ($p < 0.01$) from Pre-VF value.

TABLE 2

Hypervolemic Group (n = 6)*

	Pre-VF	First ZEEP	20 cm H_2O PEEP	Last ZEEP
pH	7.40 ± 0.01	7.43 ± 0.03	7.57 ± 0.04‡	7.50 ± 0.04†
Pa_{O_2} (mm Hg)	401 ± 81.6	281 ± 64.0†	379 ± 54.8	369 ± 67.1
Pa_{CO_2} (mm Hg)	38 ± 0.5	29 ± 3.7†	18 ± 2.0‡	19 ± 1.4‡
Base excess (meq/L)	−0.8 ± 0.6	−3.5 ± 2.1	−1.2 ± 1.5	−4.3 ± 2.0

* Values are means ± SE. Abbreviations are defined in footnote to Table 1.
† Significant difference ($p < 0.05$) from Pre-VF value.
‡ Significant difference ($p < 0.01$) from Pre-VF value.

TABLE 3

Hypovolemic Group (n = 6)*

	Pre-VF	First ZEEP	20 cm H_2O PEEP	Last ZEEP
pH	7.39 ± 0.01	7.35 ± 0.03	7.38 ± 0.03	7.29 ± 0.04†
Pa_{O_2} (mm Hg)	320 ± 56.4	241 ± 28.8†	279 ± 34.5	256 ± 23.8
Pa_{CO_2} (mm Hg)	39 ± 1.0	35 ± 0.7†	24 ± 2.2†	28 ± 3.2†
Base excess (meq/L)	−1.1 ± 0.4	−4.8 ± 1.0†	−8.4 ± 2.0†	−12.8 ± 2.4‡

* Values are means ± SE. Abbreviations are defined in footnote to Table 1.
† Significant difference ($p < 0.08$) from Pre-VF value.
‡ Significant difference ($p < 0.01$) from Pre-VF value.

is important to acknowledge that changes of CCABF, blood gas tensions and acid-base balance may not have solely been due to a given level of PEEP, rather, they may have been due to the progressive effect of the stepwise increase and decrease in PEEP levels.

In normovolemic dogs, stepwise increases in PEEP greater than 5 cm H_2O caused a progressive decrease in carotid blood flow. This may indicate that PEEP greater than 5 cm H_2O decreased venous return between chest compressions and forward blood flow decreased during chest compression despite the fact that intrathoracic pressure was increased by PEEP.

In hypervolemic dogs, it is thought that PEEP did not reduce the venous return significantly between chest compressions because of the hypervolemia. CCABF was thus increased stepwise at the time of chest compressions by an increase in intrathoracic pressure with the increase in PEEP level.

When the dogs were hypovolemic, it is speculated that the already reduced venous return due to the hypovolemia was further reduced by even low levels of PEEP, and therefore CCABF decreased significantly with increasing levels of PEEP. However, as absolute values were so small in this group, these statistically significant decreases in CCABF may not be physiologically significant. Ashbaugh and colleagues (9) have emphasized that PEEP is contraindicated in patients with low cardiac outputs. Our results also suggest that the application of PEEP in the hypovolemic state may prove deleterious during CPR.

Hodgkin and colleagues (8), in a study using normovolemic pigs, showed that the Pa_{O_2} was significantly improved and Pa_{CO_2} was significantly lower with the use of 20 torr PEEP during standard CPR. Our study also showed that dogs in all three groups were better oxygenated and more hyperventilated at 20 cm H_2O PEEP than they were during first and last ZEEP. This may have been due to an increase in the area of zone 1 in the lung (10) caused by the PEEP during CPR.

In hypervolemic dogs, hyperventilation was more pronounced and oxygenation was better than in the other two groups of dogs when PEEP was increased stepwise to 20 cm H_2O. It is obvious that volume expansion in the hypervolemic group provides a better ventilation-perfusion balance in the face of high intrathoracic pressure produced by 20 cm H_2O PEEP. Thus, the postulation by Harris and colleagues (11) seems to be important: volume expansion is indicated during external cardiac compression, even in normovolemic subjects, provided there is no pulmonary edema.

In hypovolemic and normovolemic dogs, severe metabolic acidosis developed over 18 minutes of CPR despite adequate oxygenation, indicating inadequate peripheral perfusion. On the other hand, there was only a mild metabolic acidosis in hypervolemic dogs, most likely because of better forward blood flow than in the other two groups.

In summary, PEEP has two discrepant effects on forward blood flow during standard CPR: decreasing blood flow by decreasing venous return between chest compressions, and increasing blood flow by increasing the generalized intrathoracic pressure during chest compression. The net effect of PEEP on forward blood flow depends on the state of circulating blood volume. In hypovolemic states PEEP has deleterious effects, such as reducing CCABF and causing severe metabolic acidosis during standard CPR. PEEP increases CCABF in hypervolemic states, but simultaneously it may also increase intracranial pressure, resulting in the reduction of cerebral perfusion pressure (12). Our study, however, suggests that some degree of PEEP may be beneficial in the hypervolemic patient during CPR.

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Differential Sensitivity of Fast and Slow Fibers in Mammalian Nerve
II. Margin of Safety for Nerve Transmission

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GISSEN, A. J., COVINO, B. G., AND GREGUS, J.: Differential sensitivity of fast and slow fibers in mammalian nerve. II. Margin of safety for nerve transmission. Anesth Analg 1982;61:561-9.

In a previous study it was found that concentrations of local anesthetics required to block large, fast-conducting nerve fibers were lower than those required to block small, slow-conducting fibers. The present study was instituted to evaluate the margin of safety for transmission in large versus small nerve fibers, the margin of safety being defined as the ratio between the magnitude of the action potential and the magnitude of the critical membrane potential. The effect of reducing the sodium-activating current, which reduces the magnitude of the action potential by sodium deficient solutions and tetrodotoxin application to the desheathed rabbit vagus nerve trunk (in vitro), was examined. Anode block (another method of reducing sodium current) is also discussed. In all instances, the margin of safety for transmission was greater in small, slow fibers than in large, fast fibers. The variations seen in nerve response to tetrodotoxin application are explained by the presence of nerve fiber diffusion barriers; the large fibers show more diffusion protection than the small fibers. Onset, duration, and intensity of differential nerve blockade by drugs reflect a balance between diffusion barriers and axon membrane sensitivity.

Key Words: ANESTHETICS, Local: differential sensitivity; NERVE: conduction.

RECENT STUDIES (1) have shown that fast-conducting nerve fibers, i.e., large-diameter fibers, are blocked consistently at lower concentrations of local anesthetic agents than are slow-conducting nerve fibers, i.e., small-diameter fibers. This observation appears contradictory to the usual statement in the literature. Standard textbooks repeatedly state that small fibers are more sensitive to blockade by local anesthetic drugs than are large nerve fibers (2–4). In an attempt to investigate these findings further and

possibly to provide a physiologic explanation, an evaluation of the margin of safety of nerve transmission in fast- and slow-conducting fibers is reported in these studies.

The margin of safety of transmission (also known as safety factor, safety reserve, resistance to transmission block, etc,) has been defined (5) as the ratio of the total action current of the nerve fiber to the minimum current needed for threshold depolarization (Fig 1). This level of minimum current is usually termed the critical membrane current, or threshold, necessary for nerve activation. The currents described also can be expressed as the potential difference across the nerve membrane (the transmembrane potential). If the transmembrane action potential/threshold potential ratio is less than 1.0, a propagated action potential (AP) will not follow nerve stimulation. If the ratio exceeds 1.0, an adequate nerve stimulation will produce complete membrane depolarization and nerve conduction will take place. For the largest myelinated fiber in the amphibian sciatic nerve trunk, a 4- to 7-fold safety factor has been estimated (5). It has been difficult to determine the safety factor of small nerve fibers because of technical problems, and only estimates have been possible. Paintal (6) has estimated

$$\text{MARGIN of SAFETY for TRANSMISSION} = \frac{A}{B}$$

FIG 1. Evoked-action potential (AP) in single vagus nerve fiber recorded as transmembrane potential versus time. A, Total potential change during AP measured from resting potential level; B, total potential change from resting potential to threshold potential necessary to activate membrane. Critical potential is the transmembrane potential at level of this threshold potential. Cross-hatched area under AP curve represents time of major flow of inward sodium-activating current.

that the smallest myelinated fiber has a safety factor of 20. Condouris et al (7), using a computer simulation of nerve transmission, arrived at the unexpected conclusion that their model of myelinated nerve was actually more susceptible to conduction block than the model for unmyelinated nerve. However, there are no reports estimating the safety margin of transmission in unmyelinated nerve fibers. The compound action potential (AP) represents the summation of the electrical activity of many single fibers in the nerve trunk. Experimental maneuvers that decrease individual fiber safety factor should be apparent as a decrease in the resultant AP amplitude. The type of fibers represented by a specific AP from a nerve trunk can be identified by appropriate conduction velocity measurements: a conduction velocity of 25 to 50 m/sec is believed to represent large myelinated A fibers, a velocity of 5 to 15 m/sec small myelinated B fibers, and speeds of 1.0 m/sec or less small nonmyelinated C fibers. Critical to this argument is the fact that the conduction speed of nerve fiber groups is proportionately slowed by methods decreasing sodium current. Only indirect evidence is available for this. Cold uniformly and proportionally slows fast- and slow-conducting fibers over a range from 7 to 40°C (8). Recent experiments with lidocaine in our laboratories support the same belief.

The rising phase of the AP in the single nerve fiber represents the period of maximum flow of sodium ions into the interior of the nerve fiber (9). Reduction of the inward sodium current by whatever means will reduce the magnitude of the individual fiber AP (and

also the total combined AP). The degree to which this inward sodium current can be decreased before conduction block should be a measure of the margin of safety of transmission in the nerve fiber. There are various means of decreasing the sodium-activating current, such as anode block, sodium deficient solutions, and application of tetrodotoxin (TTX) to nerve. Anodal block increases the positive charge on the outside of the nerve membrane and makes it more difficult for local currents to depolarize the membrane to the critical potential level required for AP propagation. Sodium-deficient solutions will directly reduce the number of sodium ions traversing the sodium channel following membrane activation and prevent depolarization reaching the critical membrane potential level following activation. Tetrodotoxin inhibits sodium conductance by blocking the external opening of the sodium channel (10). This report discusses the experimental results achieved using sodium-deficient solutions and TTX as a means of evaluating the safety margin of transmission in nerve fibers of various conduction velocities. We also discuss the results reported with anode block.

Methods

Rabbit vagus or sciatic nerve trunks were rapidly removed from adult albino rabbits killed by air embolus. The excised nerves were stored until use in Liley solution, at 22°C, and stirred constantly by O_2 aeration. Standard Liley solution (NaCl 136.8 mM, KCl 5.0 mM, CaCl$_2$ 2.0 mM, MgCl 1.0 mM, dextrose 11.0 mM) was buffered by the addition of 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (Hepes) 2.53 mM and pH adjusted to 7.4 by the addition of 0.1 N NaOH.

The nerve trunk was desheathed in its central portion to expose at least 10 mm of bare nerve. The nerve chamber in which the nerve was then placed has three chambers: the two lateral wells for recording and stimulation and the middle well for perfusing with the drug under examination. Electrodes of 0.38 mm bare platinum were used for stimulation and recording; the cathodal stimulation electrode was always the one closest to the central well. The lateral wells were isolated from the central chamber by petroleum jelly seals and the entire assembly could be made airtight by a screw-on cover. Complete details regarding the nerve chamber have been presented previously (1).

Experiments were carried out at room temperature (22°C), using a stimulus frequency of 0.016 Hz and stimulus intensity adjusted to provide a maximum AP on the viewing oscilloscope. Stimulus duration was

adjusted by means of separate Grass S-48 stimulators to 0.05 msec for A fibers, 0.1 msec for B fibers, and 1.0 msec for C fibers. Conduction velocities of 25 to 50 m/sec were defined as larger myelinated A fibers; 5 to 15 m/sec were defined as B fibers, and 1.0 m/sec or less were C fibers.

Liley solution for perfusion and drug solvation was prepared fresh each day from a 10X stock solution. The sodium-deficient solution was prepared by substituting an appropriate quantity of choline chloride (mole per mole) for sodium chloride. KOH, instead of NaOH, was used to adjust the buffer to 7.4 in this solution. One milligram of TTX (Astra Pharmaceutical Products, Inc.) was dissolved in 100 ml of triple distilled water and aliquots of 20 ml were rapidly frozen and stored. The aliquot for 1 day's use was thawed, dissolved in Liley solution to achieve the proper concentration, and discarded at the end of the day's experiment.

The recording electrodes were soldered to coaxial cables. The methodology for recording the AP of fast- and slow-conducting fibers has been previously described (1). The evoked nerve signal recorded on surface electrodes was then fed into a differential preamplifier (Tektronix AM502) by capacitive coupling. Preamplification was usually set at 500X gain. The output signal from the preamplification was then fed into the oscilloscope's differential amplifiers (Tektronix 5113 storage oscilloscope-5A22N differential amplifiers). AP measurements were made from polaroid photographs of the face of the storage oscilloscope.

In each experiment, a control period of 30 minutes before the experiment began assured AP stability. After 30 minutes of drug exposure, the amplitude of the resultant AP was compared with that of the control values. A wash period then returned the nerve response to at least 95% of control values. Responses of less than 5% or more than 95% of control values were discarded, as the critical value sought was the 50% point of dose-response (ED_{50}) and the adjacent linear portion of the dose-response curve. Repeated observations during the last part of the test period assured reasonable equilibration of nerve response to the test drug. (Equilibration had been reached if change of 10% or less in the AP recording occurred in the last 10 minutes.)

Results were plotted as dose-response curves with AP amplitude presented as percentage block (control value equal to zero) versus logarithm of drug concentration. Percentage of AP block was converted to probit values, and ED_{50} and standard error of the

estimate (SEE_x) were derived by a graphic method (11). SEE_x is equivalent to 1 SD. Probit conversion emphasizes the ED_{50} response point and adjacent linear region of the curve and may be used to compare different pharmacologic agents under standard conditions. By emphasizing the ED_{50} response point and adjacent portions of the dose-response curve, we avoided the severe distortion of the sigmoid response curve at response extremes, which was further minimized by discarding values less than 5% or more than 95%.

Results

Sodium-Deficient Solution

As the sodium ion concentration in Liley solution was decreased, A fibers (25 to 50 m/sec conduction velocity) in the vagus nerve trunk were the first to be blocked. Further reduction in sodium ion concentration blocked the B fibers, and finally the C fibers. ED_{50} block for A, B, and C fibers occurred, respectively, at 44.79%, 38.29%, and 27.36% of the normal sodium level of 136.8 mM Na ion. The same experiment was repeated on the rabbit sciatic nerve trunk, whose A-alpha fibers conduct at an average of 34.90 m/sec compared with 26.82 m/sec for the A fibers in the vagus trunk. The A fibers in the sciatic nerve had the least tolerance to reduction of the sodium ion concentration. ED_{50} block occurred at 60.86% of the normal sodium ion level. The Table and Figs 2 and 3 demonstrate a linear relation between ED_{50} block and the sodium ion concentration in the infusate in which the smallest, slow-conducting nerve fibers are the most resistant to the conduction blocking effect of reduced sodium ion.

TTX Block

Application of tetrodotoxin at concentrations of 0.100 to 0.010 μM to isolated desheathed vagus nerve produced a differential block of A, B, and C fibers similar to that seen with the sodium-deficient solutions. Studies exposing the desheathed isolated nerve to TTX for 30 minutes resulted in block of AP with the following values: A, 47.8% ± 24.1% (n = 16), B, 38.4% ± 25.9% (n = 17), and C, 37.5% ± 18.5% (n = 15); i.e., A fibers were blocked more than B fibers and B fibers more than C. Because it was obvious that equilibration of response in A and B fibers had not occurred in 30 minutes, studies were extended to 60 minutes and then to more than 120 minutes. No change in the final relationship of A, B, and C block

TABLE

Action Potential Response to Various Concentrations of Sodium Ion in Perfusing Solution*

Fiber	Conduct velocity	N	Sodium-deficient solutions		$\bar{X} \pm X_{SD}$	$\bar{Y} \pm Y_{SD}$
			$Na^{\pm}$ % at ED_{50}†	$ED_{50}^{\pm}$ SEE_x		
	m/sec		%		*mM Na*	*% response AP*
A^{sc}	34.90	9	60.86	85.20 ± 1.48	83.22 ± 7.45	47.00 ± 17.25
A^{va}	26.82	33	44.79	62.70 ± 1.55	58.93 ± 9.30	63.79 ± 19.11
B	6.63	19	38.29	53.60 ± 2.73	56.48 ± 9.21	36.89 ± 13.19
C	0.95	22	27.36	38.30 ± 5.67	42.24 ± 14.64	44.68 ± 21.93

* Response is correlated to conduction velocity of combined-action potential in nerve trunk. Sodium concentration is reduced by equimolar substitution of choline chloride for sodium chloride. Abbreviations used are: ED_{50}, drug concentration at 50% response (calculated); SEE_x, standard error of the estimate of X; $\bar{X}$, mean drug concentration (observed); X_{SD}, standard deviation of X; $\bar{Y}$, mean percent response of AP (observed); Y_{SD}, standard deviation of Y; A^{sc}, A fibers in sciatic nerve; A^{va}, A fibers in vagus nerve.

† Normal = 136.8 mM sodium.
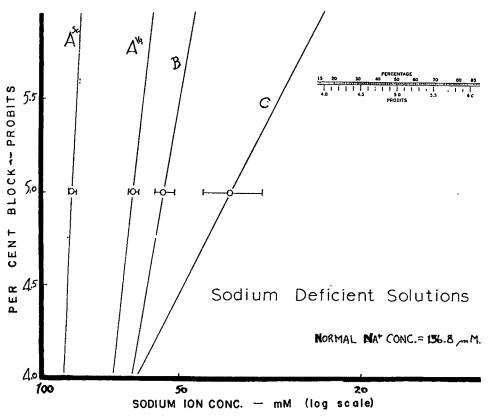
FIG 2. Plot of percent block of AP (as probits) versus sodium ion concentration in Liley's solution. Sodium ion is replaced by choline ion. A^{sc} (sciatic nerve), A^{VA} (vagus nerve), B, and C fiber groups are as classified in text. E_{50} = standard error of the estimate of x determined by graphic method (11). Note that sodium ion concentration decreases to right margin.

occurred at any of these increased exposure times. However, it was questionable that drug nerve equilibration in the A and B fibers had occurred even at these prolonged periods. It is interesting to note here that Colquhoun et al; (12) reported in one study of TTX that equilibration took more than 6 hours at concentrations less than 0.010 μM. In Fig 4 we present one typical experiment with TTX when 0.010 μM was applied for 180 minutes. Several features of the re-

sponse are notable at this TTX concentration: (a) A and B fibers show block at this TTX concentration, (0.010 μM), C fibers show no block at all; (b) slow B fibers block earlier than faster A fibers; (c) fast A fibers reach a more profound level of block with time than the B fibers; and (d) washing the preparation with perfusion fluid free of TTX seems to have no effect and the block of A and B fibers progresses. This was not due to nerve fiber deterioration. Storage

in TTX-free solutions for 12 hours returned nerve response to 85% of control values. A similar experiment with TTX at a concentration of 0.015 μM is presented in Fig 5. In this experiment, at a higher concentration of TTX, C blocked first, then B, then A. However, again with time, A showed a more
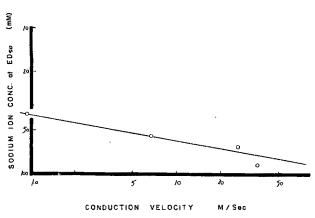
FIG 3. Log plot of sodium ion concentration at ED_{50} point versus log of nerve conduction velocity. Note that sodium concentration decreases upward from origin.

profound block than B, and B a more profound block with C. Application of TTX at concentrations of 0.40 μM and greater caused rapid and profound block of all three groups of nerve fibers.

Discussion

Numerous investigations have already reported that anodal block inhibits conduction in large, fast-conducting nerve fibers while still permitting transmission in smaller, slow-conducting nerve fibers (13–18). Results reported by Fukushima et al (18) plotted on double-log coordinates (Fig 6) demonstrate an inverse linear relationship between the magnitude of the blocking anode current and the conduction velocity of the nerve fiber; large fibers required a lower current level for blockade than small fibers. A comparison of this plot with Fig 3, which shows sodium ion level in the infusion at ED_{50} block versus nerve conduction velocity, also demonstrates that the slower the conduction velocity the greater the ability of the fiber to maintain transmission under adverse conditions.

Results with (a) sodium-deficient solutions, (b) low
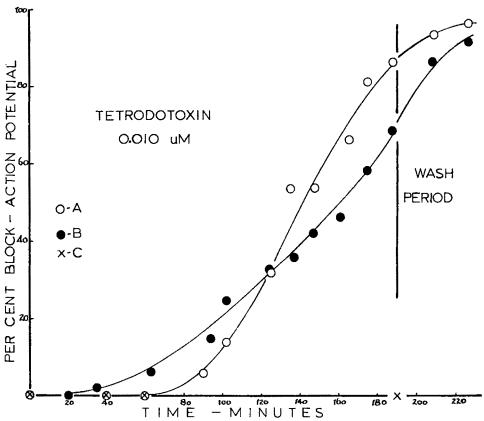
FIG 4. Example of effect of tetrodotoxin (TTX) at 0.01 μM concentration applied to A, B, and C fibers for 180 minutes as measured by evoked AP. At "wash" period TTX was removed

from perfusing solution. Note lack of change in A and B response at wash and continued progression of block.

TETRODOTOXIN

0.015 uM

PER CENT BLOCK — ACTION POTENTIAL

O - A
● - B
✗ - C

TIME — MINUTES
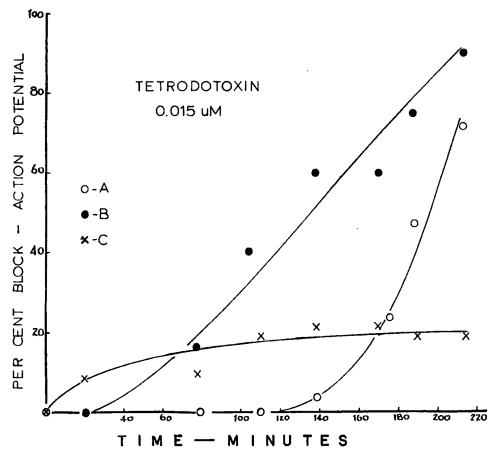
FIG 5. Example of effect of TTX at 0.015 μM concentration on A, B, and C fibers for 220 minutes as percent change in AP amplitude (0 = no block at control level).

concentration and long applications of TTX, and (c) anodal block support the thesis that the margin of safety for transmission is greater in small, slow-conducting fibers than in large, fast-conducting fibers. As conventional local anesthetics act primarily by inhibiting sodium conductance, these agents should reduce the safety factor for nerve transmission in a fashion similar to the above maneuvers. Our previous studies show that the conventional local anesthetics block fast-conducting nerve fibers before blocking slow-conducting fibers. Thus both sets of experiments could be interpreted as indicating that large, fast fibers have a lower safety margin for transmission than small, slow nerve fibers (1). These studies do not permit evaluation of the basic causes for the differences in safety factor among the three types of nerve fibers. It would be surprising if the marked anatomic differences between large myelinated fibers, small myelinated fibers, and nonmyelinated fibers did not also reflect significant physiologic and pharmacologic differences. Exact delineation of the basic causes for

these pharmacologic differences will have to await studies using single nerve fibers from each group.

The results with TTX are notable for their marked difference from those seen with the sodium-deficient solutions. The sodium-deficient experiments reached equilibration of response in 30 minutes, recovery followed rapidly when normal sodium solution was used following block, and the relative susceptibility of A, B, and C to fiber block by sodium deficiency was the same at the beginning and the end of the experimental period. On the other hand, the TTX experiments did not fully equilibrate even after 3 hours of drug exposure; a long period of drug-free wash was necessary before recovery from block took place and, most notable, during the early stages of drug exposure the C fiber was blocked first, then the B fiber, finally the A fiber. The reverse order of fiber block (A, B, and then C) was apparent at the end of the period of drug exposure. This final relationship is, of course, the order of susceptibility seen with local anesthetic drugs and sodium-deficient solution in all
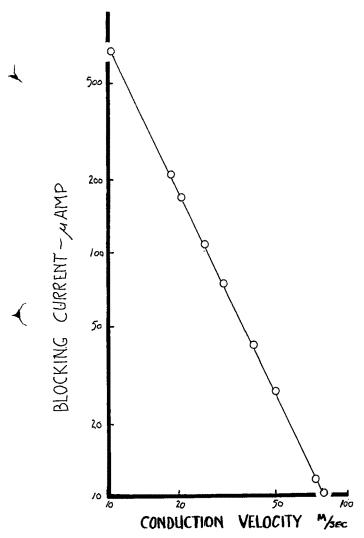
FIG 6. Log-log plot of blocking anode current versus conduction velocity of myelinated nerve fibers calculated from Fukushima et al (18).

the previous experiments. Yet TTX is believed to have its only pharmacologic effect on the membrane sodium ion mechanism (10). Colquhoun and Ritchie (11) reported equivalent and additive effects of sodium-deficient solutions and TTX. However, their study examined only the nonmyelinated C fibers. Determination of correlation coefficients in our experiments for A, B, and C fibers relating TTX concentration (0.100 to 0.010 μM) and nerve response (after 30 to 120 minutes of drug exposure) reveal a poor relationship for A and B fibers, but a much more marked positive correlation (r) for C (r_A = 0.031, r_B = 0.035, r_C = 0.57). Thus, additional factors may be involved in the block of A and B fibers by TTX as compared with the effect of TTX on C fibers.

TTX is known to diffuse poorly through the covering sheaths of nerve fibers. A review of the histology of various nerve fibers may help explain some of the apparently contradictory results with TTX. The nodes of Ranvier in large myelinated fibers represent the sites of membrane activation in saltatory conduction (5). The original drawings of Ranvier (20) and other light microscopists depict this area as devoid of any significant anatomical coverings and "open" to the surrounding tissues. The recent use of electron microscopy and electron scanning techniques have shown a complex array of microstructures in this "intermyelin" space between the axon membrane surface and the outside of the nerve fiber (21). The adjacent layers of Schwann cell do not terminate at this nodal space, as usually depicted, but project multiple fine processes ("fingers") termed microvilli into this space. The number, complexity, and depth of these microvilli increase as the number of myelin layers increases. In addition, a matrix of structureless ground substance has been demonstrated between the microvilli (22). This matrix contains a large amount of mucopolysaccharides which possess many molecular negative charges and act as an "ion sink" for substances with positive charges.

Molecules such as TTX, which are lipid insoluble and exist mainly in a charged cationic form, would be impeded in diffusing from outside the nerve to the nodal nerve membrane, both by membrane barriers formed by the intertwining microvilli from the Schwann cell layers and by adsorption onto the negatively charged sites of the mucopolysacccharides. In addition, an unstirred layer of extracellular fluid exists between the innermost layer of microvilli in the nodal space and the axon membrane surface which is a further obstacle to diffusion of TTX to the sodium channels in the membrane.

Let us examine the sequence of diffusion following the application of an appropriately high concentration of TTX to a mixed nerve trunk. The drug applied to the outside of the nerve trunk will penetrate to the endoneural space between the various nerve fibers. Because of differing depth of diffusion barriers on the A, B, and C nerve fibers, TTX will reach the axonal surface of the smallest fibers (C) first in significant concentration and so cause C fiber conduction block first. As the TTX concentration increases at the various nodal membrane surfaces, B and, finally, A will show fiber blockade. The transmission blocking properties of TTX represent a balance between the drug diffusion factors and the axonal membrane sensitivity of the nerve fibers represented by the safety margin

of transmission. We postulate that diffusion barriers are greatest in the large, fast-conducting fibers and least in the small, slow fibers, whereas safety margin of transmission is least in large fibers and greatest in small fibers.

If the concentration of TTX applied is low, the relatively high safety margin of the nerve membrane in the C fibers will preclude transmission block in the presence of such a low TTX concentration. However, prolonged application of such a low TTX concentration will ultimately diffuse through the barriers of the large A fibers and will eventually cause conduction block due to the low safety margin of A fibers (Fig 4).

Only one molecule of TTX is required to block one sodium channel (23) so that concentration requirements at the membrane surface are small and TTX shows extremely high potency and rapid onset of drug effect (12) in isolated single nerve fibers. Studies of single myelinated nerve fiber (squid, amphibian, and mammal) under voltage clamp techniques show that indeed the time of latency between drug application and onset of effect is short. This is to be expected as most of the epineurium and perineurium fascial layers have been removed. However, even with this short onset time, it is believed that drug diffusion rather than drug-receptor reaction time determines the latency of TTX, i.e., the onset of TTX effect is diffusion limited.

There are other membrane-active drugs whose chemical characteristics simulate TTX and that also show limitation of free access to the nerve membrane in large myelinated nerve. Acetylcholine and curare are relatively lipid insoluble, almost completely ionized (cations) at pH 7.4, and extremely potent in small concentrations. Although both drugs are extremely effective at the neuromuscular junction, they are without effect when applied to mammalian myelinated nerve. Dettbarn (24) found, however, that if nerves were pretreated with phospholipase enzymes (A or D), these drugs then demonstrated an effect on the evoked action potential. The enzymes caused dissolution of surface membranes whose main component was phospholipids. Even though extensive lysis had occurred, normal nerve function continued. It was also shown that TTX binding sites on the membrane were only minimally reduced after treatment with phospholipase C or D (25). Ritchie (26) subsequently demonstrated that, although acetylcholine had no effect on the function of large, myelinated nerves, it definitely affected the action potential of nonmyelinated nerve, even without enzyme treatment. Although this was not the intent of the experiments,

they show the presence of more effective drug barriers in myelinated than in nonmyelinated nerve.

Further evidence for drug barriers in nerve may also be found in neurophysiologic studies. The Hodgkin-Huxley explanation of excitable membrane function explains the action potential as a function of sodium and potassium ion movements through the membrane (9). Post-peak AP currents, as represented by repolarization and after-potentials, have been ascribed to potassium ion movement. After-potentials (and thus K^+ ion movement) are readily apparent in unmyelinated C fibers or squid axon, but not in large, myelinated mammalian nerve fibers. Frankenhaeuser and Hodgkin, studying potassium ion movements in the squid axon, explained the quantitative results by the presence of a diffusion barrier (or an unstirred fluid layer, or both) (27). Direct evidence for such a barrier has recently been reported by Chiu and Ritchie (28). Treatment of large nerve fibers in the rabbit vagus with hyperosmotic solutions and collagenase enzymes resulted in the appearance of potassium after-potentials following nerve activation (28). It was felt that this treatment loosened membrane barriers at the axon surface.

The theory that the matrix at the node of Ranvier acts as an ion sink for positive charged ions is well supported by work by Langley and London, reporting local anesthetics, dyes, and metal ions concentrating in this matrix material (29–32).

There are no reports of differential effects in various sizes of nerve fibers from the viewpoint of drug diffusion limitation except for the one by Ritchie (26). The various reports cited above do imply, however, that there are significant barriers to the diffusion of membrane-active drugs from outside the nerve fiber (especially in large myelinated nerve fibers). The results of the TTX experiments appear logical based on the concept of extensive diffusion barriers in large myelinated nerves. The balance between nerve diffusion barriers and membrane sensitivity of A, B, and C fibers may also explain the differential sensory/motor effects of various clinically used local anesthetics such as bupivacaine and etidocaine.

These experiments indicate that a single number (such as embodied in C_m-minimal drug concentration) cannot accurately indicate local anesthetic drug potency. The safety margin of transmission for each group of fibers must be known. Also the drug diffusion characteristics must be known, especially lipid solubility and degree of ionization. It is possible in isolated nerve experiments, by manipulation of drug concentration and duration of nerve exposure, to

make A, or B, or C more profoundly and rapidly blocked than the other fibers. Evaluation of differential nerve susceptibility to local anesthetic block can only be done by evaluating the effects of various drug concentrations and durations of exposure. We present such a study for etidocaine and bupivacaine in the succeeding paper (33).

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Differential Sensitivity of Fast and Slow Fibers in Mammalian Nerve
III. Effect of Etidocaine and Bupivacaine on Fast/Slow Fibers

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Etidocaine and bupivacaine are long-acting local anesthetics with contrasting effects on motor and sensory function. The effect of these drugs on fast-conducting (large, motor) and slow-conducting nerve fibers (small, pain) in the isolated rabbit vagus nerve was examined. Both drugs had an equivalent effect on slow fibers. Etidocaine had a short latency and bupivacaine a prolonged latency of effect on fast fibers. During this long latency of effect by bupivacaine on fast fibers, only the slow fibers were blocked. This period of differential effect on fast and slow fibers is believed to be the explanation for the early effect of bupivacaine on pain fibers followed by a later block of motor function. This difference is believed to be due to the lower lipid solubility and greater ionization of bupivacaine, which impedes diffusion across the permeability barriers present in fast-conducting A fiber.

ETIDOCAINE and bupivacaine are long-acting local anesthetic drugs with interesting and contrasting clinical characteristics that may be related to differences in physiochemical properties (1). Bupivacaine possesses a higher pKa (8.1) than etidocaine (7.7) and so is more ionized at physiologic pH. Bupivacaine is also less lipid soluble than etidocaine (2). Our previous report (3) demonstrated differences in the safety margin of transmission in various nerve fibers and indicated that fast- and slow-conducting fibers differ significantly in terms of diffusion barriers to externally applied membrane active drugs. In this study (3), the activity of tetrodotoxin was studied and its differential effect on nerve fibers was related to

safety margin of nerve transmission, diffusion barriers, lipid solubility, and degree of ionization of tetrodotoxin. In the present report, similar studies have been conducted with bupivacaine and etidocaine in an effort to explain the differential effects on sensory and motor functions seen following clinical use of these local anesthetics.

Methods

The method of study was the same as presented previously (3) except that the nerve trunk was not desheathed. Under microscopic dissection all adventitial material was removed, leaving the nerve sheath intact and clean.

Etidocaine and bupivacaine were obtained as pure powdered base (supplied by Astra Pharmaceutical Products Company), dissolved in Liley solution at the indicated concentration, and discarded at the end of the day. The nerve trunk was exposed to drug by a slow perfusion of oxygenated solution at 0.1 ml/min. Perfusion was necessary because of the long periods of drug exposure in some experiments (3 to 4 hours).

Two sets of experiments were performed. Initially, a concentration of 8.0 mM bupivacaine and etidocaine (approximately 0.25% solution) was used. The rate

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and degree of block were observed for A and C nerve fibers; subsequent recovery with drug-free perfusion was also followed for a prolonged period of observation. In the second set of experiments, the effect of various concentrations of bupivacaine and etidocaine (0.04 to 2.00 mM) on the degree and time of block of A and C fibers was studied.

Results

At a concentration of 8.0 mM (0.25% solution) bupivacaine and etidocaine caused a 100% block of A fibers (conduction velocity 25 to 50 m/sc) and 80% block of C fibers (conduction velocity 1.0 m/sec or less) within 3 minutes (Fig 1). Little difference in onset and degree of block was noted with the use of 8.0 mM bupivacaine and etidocaine.

Striking differences between etidocaine and bupivacaine were noted during the recovery phase from the above block during a prolonged period of perfusion with drug-free solution (Figs 2 and 3). The course of recovery from block of the action potential (AP) of C fibers is essentially the same with both etidocaine and bupivacaine during the 100-minute observation period; approximately 20% block remains after 100 minutes of washout of C fibers in both instances. The half-time constant of recovery (to 63% of final value) for C fibers is 29 minutes following application of etidocaine and 27 minutes following bupivacaine. Note, however, that the recovery of A fiber function was markedly prolonged following bupivacaine application as compared to the recovery following application of etidocaine. AP of A fibers following etidocaine application recovered to the level of 20% block (same as C fibers) in 100 minutes of wash. However, following bupivacaine application, recovery had only reached 60% by 100 minutes of washout. Also to be noted is the prolonged latency before recovery began following bupivacaine application with both A and C fibers; 100% block of both A and C persisted over 25 minutes into the washout period. At this concentration the differential effect of etidocaine and bupivacaine is not apparent (this is also true in the clinical situation).

We proceeded to evaluate the effect of etidocaine and bupivacaine at lower concentrations than used above. Because of difficulty in achieving equilibration of A fiber response, we selected the ED50 level of A fiber block to evaluate C fiber response as to degree of block and time needed to reach this point. Fifteen separate fiber experiments were performed at drug concentrations of 0.075 to 0.50 mM, approximately equally distributed between etidocaine and bupiva-
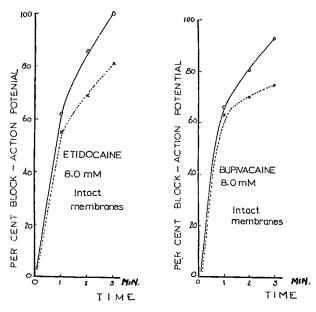
FIG 1. Rabbit vagus, not desheathed, at 22°C. Percent block of action potential (AP) amplitude following application of 8.0 mM etidocaine or bupivacaine in four experiments. Dashed line, C fiber AP response; solid line, A fiber AP response.

caine. At the ED50 point of A fiber response, C fiber response following bupivacaine was 33.4% ± 8.9% blockade compared with 16.2% ± 6.7% blockade following etidocaine. Note that the clinical evaluation of bupivacaine and etidocaine is that bupivacaine is a more effective blocker of pain (possibly C fibers) whereas etidocaine more effectively blocks motor function (possibly A fibers). Bupivacaine took longer to reach this degree of block of A and C fibers then etidocaine (38.9 ± 23.6 minutes versus 7.8 ± 7.2 minutes). Clinically, onset of etidocaine block (both motor and sensory) is more rapid than bupivacaine.

In many of these drug studies at low concentrations (etidocaine and bupivacaine concentrations varied between 0.04 to 0.30 mM) it was noted that C fiber showed equilibration block first. An A fiber block took longer to manifest itself but invariably reached a more profound level of equilibration block than C fibers. An average of 5.1 minutes was required for the A block to exceed the C block in the presence of etidocaine. In fibers exposed to bupivacaine 79.2 minutes was required for this "cross-over" point. The apparent difference in behavior is due to the long latency of the A fiber response following application of bupivacaine. The C fiber response to etidocaine and bupivacaine is approximately equivalent. A composite plot based on 14 experiments showing this A and C fiber response to drug application is presented in Fig 4.
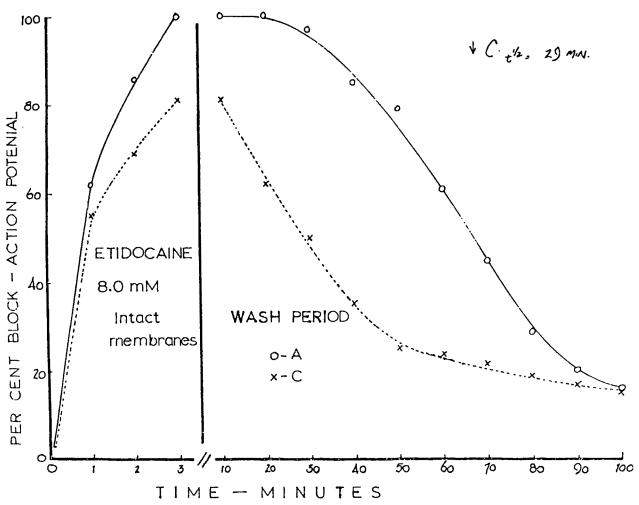
FIG 2. Recovery of A and C fibers following application of 8.0 mM etidocaine for 3 minutes. Half-time constant (time for 63% recovery) of C fiber = 29 minutes. Dashed line, C fiber AP response; solid line, A fiber AP response.

Discussion

The results of this study indicate that the differential effect on peripheral nerve fibers by etidocaine and bupivacaine is only apparent at selected low concentrations and only in the presence of significant diffusion barriers (such as an intact perineurium). Desheathed vagus nerve trunk exposed to a high concentration of etidocaine or bupivacaine for a limited time period showed no differential effect (4). Moreover, the different response of nerve to the application of etidocaine and bupivacaine appears related primarily to the large fast-conducting myelinated nerve fibers and not to the response of the small slow-conducting nonmyelinated nerve fibers. From this viewpoint one can say that the behavior of bupivacaine versus etidocaine is primarily due to the slow onset of effect of bupivacaine on motor fibers (fast) rather than a primary effect on pain fibers (slow). The

effect of bupivacaine and etidocaine on slow fibers (C fibers) is almost equivalent at both high and low concentrations. That is, the local anesthetic bupivacaine has a time-limited pharmacologic effect on large, fast, myelinated A nerve fibers. It is essentially a slow blocker of motor function.

The differential blocking effect of bupivacaine on A and C fibers has many similarities to that presented previously for tetrodotoxin (TTX). As suggested to explain the effect of TTX, A fibers have greater diffusion barriers than C fibers (3). Drugs with low lipid solubility and high ionization when applied outside the nerve trunk are limited in their penetration to the nerve membrane of A fibers compared to the rate of penetration to the C fiber membrane. Comparison of the results in experiments with etidocaine and bupivacaine at intermediate and low concentrations indicate that these drugs do reach the membrane of the C nerve fiber rather rapidly as is shown in Fig
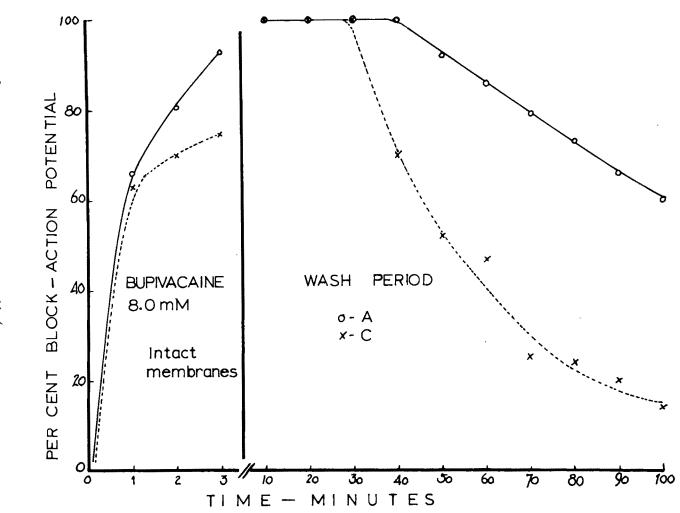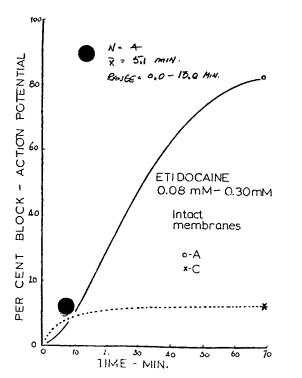
FIG 3. Recovery of A and C fibers following application of 8.0 mM of bupivacaine for 3 minutes. Half-time constant (time for 63% recovery) of C fiber = 27 minutes. Dashed line, C fiber AP response; solid line, A fiber AP response.
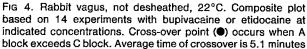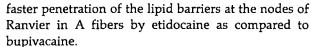
4. However, bupivacaine reaches the nerve membrane of the A fiber more slowly than etidocaine so that the cross-over point takes longer with bupivacaine (Fig 4). However, the A fiber barrier is not impenetrable. High concentrations of bupivacaine and etidocaine cause rapid block of both A and C fibers (Fig 1). Following this exposure to high drug concentrations, the diffusion barriers in the A fiber (which limit drug diffusion in both directions) limit drug removal during the washout period, and in comparison to the A fiber recovery following etidocaine application a slow recovery of A fibers is observed following bupivacaine application (Figs 2 and 3).

These differences are probably related to the physiochemical properties of the two agents. Bupivacaine has a pKa of 8.1, which means that 80% of the molecules exist in the ionized state and 20% in the nonionized base form at a physiologic pH of 7.4. By contrast, etidocaine has a pKa of 7.7 so that only 65% exists in the ionized form and 35% in the unionized form at pH 7.4 (2). As shown by Ritchie, Ritchie, and Greengard (5), the unionized base form of local anesthetics diffuses most rapidly across the nerve sheath. The ionized moiety has difficulty penetrating lipid membranes. These differences in pKa and degree of ionization between bupivacaine and etidocaine probably explain the more rapid onset of A fiber block with etidocaine as A fibers have protective tissue barriers that severely limit drug access by the bupivacaine molecule to the A fiber nerve membrane. The lesser tissue barriers surrounding C fibers probably explain the ease and rapidity of C fiber block with both bupivacaine and etidocaine. Further, the lipid partition coefficient of bupivacaine has been reported to be 30 compared to a value of 140 for etidocaine (2). This would further tend to favor the
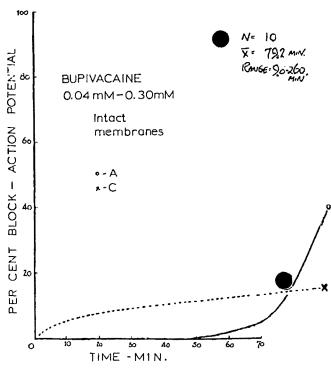
Fig 4. Rabbit vagus, not desheathed, 22°C. Composite plot based on 14 experiments with bupivacaine or etidocaine at indicated concentrations. Cross-over point (●) occurs when A block exceeds C block. Average time of crossover is 5.1 minutes following etidocaine application and 79.2 minutes following bupivacaine application. Dashed line, C fiber AP response; solid line, A fiber AP response.

faster penetration of the lipid barriers at the nodes of Ranvier in A fibers by etidocaine as compared to bupivacaine.

Considerable differences obviously exist between the isolated nerve in vitro and the human clinical situation. However, it is interesting to speculate on the basis for the clinical differences observed between bupivacaine and etidocaine shown in these in vitro studies. Bupivacaine is particularly useful in obstetrics (to block pain but still maintain muscle function). This differential effect is best noted in clinical situations at low concentrations of bupivacaine, i.e., 0.125% to 0.25%, applied by epidural technique (to increase diffusion barriers). This would correspond to the long cross-over effect in A and C nerve fibers noted to follow application of low concentrations of bupivacaine to the isolated nerve in these experiments (Fig 4). A similar situation occurs in peripheral nerve blocks with bupivacaine, in which it is a common occurrence to have adequate pain block but inadequate block of motor function. On the other hand, it is difficult to separate the sensory and motor blocking activity of etidocaine. In addition, etidocaine is characterized clinically by a rapid onset time, especially for motor blockade. This again, is similar to the in vitro nerve situation seen in these experiments in

which the time for cross-over effect between A and C fibers was short for etidocaine (Fig 4).

We continue to investigate the effect of the physiochemical properties of drugs on differential block of the mixed peripheral nerve. In our first study (4) we demonstrated that small slow-conducting fibers (which could include unmyelinated pain sensation fibers) consistently required a higher concentration of local anesthetic drug to block transmission than large fast-conducting fibers. This made it seem unlikely that anesthetic drugs could be used to block pain sensation and still maintain motor function. A subsequent study (3) showed that large fast-conducting fibers demonstrated significantly greater drug diffusion barriers at the sites of axon membrane activity than did slow-conducting fibers. This was especially true for drugs with low lipid solubility and a high degree of ionization at physiologic pH. We believe that this would permit clinical and pharmacologic maneuvers that would allow block of pain sensation but permit motor function, at least for a period of time.

The early onset of C fiber block preceding the delayed onset of A fiber block with bupivacaine seen in these experiments makes it likely that during this early period pain sensation is blocked while motor

function is still relatively intact. This delayed onset of A fiber block by bupivacaine compared to the rapid onset of A fiber block by etidocaine seen in these studies may be the explanation for the rapid and profound motor block seen in clinical situations with the use of etidocaine.

The above results suggest further investigation of drugs with high pKa and low lipid solubility as agents that may be clinically useful in producing differential nerve block, i.e., control of pain while still maintaining adequate motor function.

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Oxygen Transfer from Mother to Fetus during Cesarean Section under Epidural Anesthesia

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RAMANATHAN, S., GANDHI, S., ARISMENDY, J., CHALON, J., AND TURNDORF, H.: Oxygen transfer from mother to fetus during cesarean section under epidural anesthesia. Anesth Analg 1982;61:576-81

The correlation between maternal Pa_{O_2} levels and umbilical vein (UV) and umbilical artery (UA) P_{O_2} levels was studied in 40 healthy patients undergoing elective cesarean sections under lumbar epidural anesthesia. Patients were divided into four equal groups. Each group inhaled oxygen at a $F_{I_{O_2}}$ of 0.21, 0.47, 0.74 (in nitrogen), or 1.0. Maternal arterial samples and fetal UV and UA samples were collected at the time of delivery. Maternal Pa_{O_2} levels increased from 96 ± 4 (1 SE) torr during exposure to a $F_{I_{O_2}}$ of 0.21 to 232 ± 6, 312 ± 16, and 423 ± 6 torr while breathing $F_{I_{O_2}}$ of 0.47, 0.74 and 1.0, respectively. UV P_{O_2} levels increased from 28 ± 1 to 36 ± 1.5, 41 ± 1.3 and 47 ± 1.2 torr in the hyperoxic groups. UA P_{O_2} levels increased from 15 ± 0.7 to 19 ± 0.8, 21 ± 0.3, and 25 ± 1.8 torr, respectively. Oxygen saturation and blood O_2 contents increased in maternal and fetal blood. Maternal arterial, UV, and UA base excess values in the hyperoxic groups were significantly higher than in the normoxic groups. There was no difference in 1- or 5-minute Apgar scores between the normoxic and hyperoxic groups. It is concluded that maternal hyperoxia improves fetal oxygen stores and acid-base status during cesarean section under epidural anesthesia.

Key Words: ANESTHESIA: obstetric; ANESTHETIC TECHNIQUES: epidural.

A CONTROVERSY exists concerning the relation between fetal and maternal oxygen tension during cesarean sections performed under general anesthesia. Rorke et al (1) found that fetal P_{O_2} levels decreased when maternal Pa_{O_2} levels were greater than 300 torr. Other authors (2, 3) have reported that fetal P_{O_2} levels did not decrease but reached a plateau when maternal Pa_{O_2} levels increased to greater than 300 torr. Our study assesses the effect of changes in maternal Pa_{O_2} levels ranging between 70 and 490 torr on fetal P_{O_2} levels during cesarean sections performed under epidural anesthesia.

Methods

Forty healthy patients (weight = 71 ± 3 kg, age = 33 ± 3 years, mean ± 1 SD) without obstetric complications were studied. All were scheduled for elec-

tive repeat cesarean sections. The protocol was approved by the Committee on Human Experimentation of the New York University Medical Center. Informed consent was obtained from all patients.

During the preoperative visit, all patients rehearsed breathing through an anesthesia face mask lightly attached to the face with a head strap to allay apprehension associated with mask breathing. On the morning of surgery all patients received 1200 ml of Hartman's solution intravenously. A Portex epidural catheter was advanced 2 cm cephalad into the epidural space through L3-4 interspace. Epidural anesthesia was induced to T-4 sensory level using 18 ± 3 ml of bupivacaine (0.75%). Left uterine displacement was maintained with a sandbag wedged under the right hip.

Patients were randomly assigned to one of the following $F_{I_{O_2}}$ groups: 0.21, 0.47, 0.74, or 1.0 (10 patients per group). Oxygen was administered by mask immediately after the epidural injection. The gas mixture was delivered from an anesthesia machine at a fresh gas flow rate of 10 L/min through a circle absorber system. When $F_{I_{O_2}}$ levels of 0.21, 0.47, and 0.74 were studied, the machine oxygen was diluted by nitrogen delivered to the common gas outlet from a calibrated flowmeter. The $F_{I_{O_2}}$ was measured within

the face mask by introducing the sampling line of a Beckman D2 paramagnetic oxygen analyzer through a T-piece inserted between the Y-piece of the anesthesia circuit and the face mask. Maternal blood pressure was monitored by sphygmomanometry. A maternal arterial (MA) blood sample was obtained from the radial artery at the time of uterine incision. Fetal umbilical arterial (UA) and venous umbilical (UV) samples were collected from a loop of umbilical cord doubly clamped before the infant's first breath (2). All blood samples were immediately analyzed for pH and blood gas tension on a Corning 175 automatic pH/blood gas analyzer (Corning Medical and Scientific Co, Medfield, MA). A manual two-point calibration was performed before analyzing each sample. Electrode performance was routinely verified using a buffered bicarbonate solution equilibrated with known concentrations of oxygen and CO_2 (Corning Confirm quality control). Blood hemoglobin concentration was measured using the cyanmethemoglobin method. The intervals between anesthetic induction and delivery (ID interval) and between uterine incision and delivery (UD interval), as well as 1- and 5-minute Apgar scores were noted.

Fetal oxyhemoglobin saturation was calculated from Nelson's equation (4) after correction of the oxyhemoglobin dissociation curve for H^+- and CO_2-induced shifts (5). Kelman's computer subroutine was used to derive maternal oxyhemoglobin saturation (5, 6). Maternal and fetal blood oxygen content was calculated using Gregory's values for oxygen capacities of the respective hemoglobin (6, 7). Maternal and
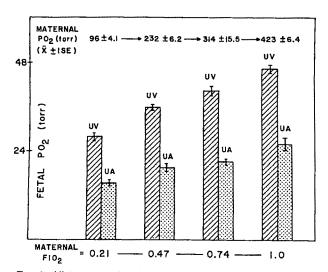
fetal base excesses at 3 g hemoglobin level (BE$_3$) were calculated by Severinghaus's BE$_3$ equation (8). The extracellular fluid (ECF) behaves as if it contained 2 to 5 g of hemoglobin (an average of 3 g) throughout the body for a wide range of blood hemoglobin concentration for both adults and the newborn. The BE$_3$ equation that estimates ECF BE at 3 g hemoglobin concentration is particularly suited for infants and anemic subjects (8). Results were expressed as means ± 1 SEM.

A combined four-group analysis of variance (ANOVA) was used to identify discriminant measurements. Each statistically significant measurement from the normoxic group was then compared with those of the hyperoxic groups by ANOVA. In addition, all hyperoxic values were compared with each other. Statistical significance was assessed at values of $p < 0.05$. Regression analysis was performed between levels of maternal Pa_{O_2}, and UV and UA P_{O_2}.

Results

Discriminant Variables

Maternal Pa_{O_2} values were 96 ± 4, 232 ± 6, 312 ± 16, and 423 ± 6 torr at maternal F_{IO_2} of 0.21, 0.47, 0.74, and 1.0, respectively (Fig 1). The corresponding UV P_{O_2} values were 28 ± 1, 36 ± 1.5, 41 ± 1.3, and 47 ± 1.2 torr, and UA P_{O_2} values were 15 ± 0.7, 19 ± 0.8, 21 ± 0.3, and 25 ± 1.8 torr, respectively (Fig 1). Both UV P_{O_2} and UA P_{O_2} values correlated closely with maternal Pa_{O_2}: UV P_{O_2} = 0.055 × maternal Pa_{O_2} + 23 ($r = 0.9$); UA P_{O_2} = 0.032 × maternal Pa_{O_2} + 12 ($r = 0.76$) over a maternal Pa_{O_2} range of 70 to 490 torr (Fig 2). With increasing maternal F_{IO_2}, maternal oxyhemoglobin saturation and total blood oxygen content increased significantly (Table 1). The mean fetal UV

FIG 1. Histograms showing umbilical vein (UV) and umbilical artery (UA) P_{O_2} levels at different maternal levels of F_{IO_2}. Maternal Pa_{O_2} levels at four levels of F_{IO_2} is shown at top. Values are means ± 1 SE (n = 10).
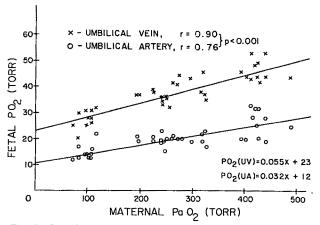
FIG 2. Correlative plot between levels of maternal Pa_{O_2} (abscissa) and umbilical vein and arterial P_{O_2} (ordinates).

TABLE 1

Oxyhemoglobin Saturation (S_{O_2} [%]) and Total Blood Oxygen Contents (CBO_2 [ml/100 ml] of blood) in Maternal Artery, Fetal Umbilical Vein, and Umbilical Artery with Different Maternal Levels of F_{IO_2}*

Maternal F_{IO_2}	Maternal artery		Fetal vein		Fetal artery	
	S_{O_2}	CBO_2	S_{O_2}	CBO_2	S_{O_2}	CBO_2
0.21	97.00 ± 0.38	15.90 ± 0.37	65.0 ± 2.7	13.16 ± 0.53	26.40 ± 26.40	5.25 ± 0.60
0.47	99.60 ± 0.06	16.70 ± 0.02	78.5 ± 0.8	15.90 ± 0.80	39.80 ± 2.20	7.90 ± 0.40
0.74	99.80 ± 0.02	16.99 ± 0.05	82.8 ± 1.4	16.80 ± 0.28	46.35 ± 1.80	9.10 ± 0.30
1.00	99.90 ± 0.001	17.35 ± 0.04	87.3 ± 0.7	17.70 ± 0.14	59.40 ± 4.10	11.75 ± 0.81

* Values are means ± 1 SE from 10 patients. Levels of significance are given in Table 2.

TABLE 2

P_{O_2} Values, Oxyhemoglobin Saturation (S_{O_2} [%]), and Total Blood Oxygen Contents (CBO_2) in Maternal Artery and Fetal Umbilical Vein and Artery at Different Levels of Maternal F_{IO_2} by Analysis of Variance*

Matenal F_{IO_2} groups compared	Maternal artery			Fetal vein			Fetal artery		
	P_{O_2}	S_{O_2}	CBO_2	P_{O_2}	S_{O_2}	CBO_2	P_{O_2}	S_{O_2}	CBO_2
0.21 vs 0.47	3	3	3	3	3	3	3	3	2
0.21 vs 0.74	3	3	3	3	3	3	3	3	3
0.21 vs 1.00	3	3	3	3	3	3	3	3	3
0.47 vs 0.74	1	3	3	2	1	1	1	1	1
0.47 vs 1.00	3	3	3	3	3	2	3	3	3
0.74 vs 1.00	2	3	3	3	2	3	2	2	2

* Numbers 1, 2, and 3 represent $p < 0.05$, 0.01, and 0.001, respectively.

oxyhemoglobin saturation increased from 65% to 87.3% when maternal F_{IO_2} increased from 0.21 to 1.0 torr. Similarly fetal UA oxyhemoglobin saturation increased from 26.4% to 59.4%. Total blood oxygen contents of both UV and UA also increased significantly (Table 1). In Table 2 is described the statistical significance of P_{O_2}, oxyhemoglobin saturation, and total blood O_2 contents in MA, UA, and UV at all levels of F_{IO_2}. Base deficits in MA, UV, and UA in the normoxic subjects were larger than in all hyperoxic patients. However, it failed to differ among the hyperoxic groups (Tables 3 and 4). UV and UA P_{CO_2} values in the normoxic groups were lower than those of the hyperoxic groups (which did not vary among themselves) (Tables 3 and 4).

Nonsignificant Variables

These included maternal P_{aCO_2} and pH, UA and UV pH values, ID and UD intervals (Table 5), mean maternal blood pressure, and maternal, arterial and fetal UV and UA blood hemoglobin concentrations. The mean maternal hemoglobin concentration for all patients studied was 12.5 ± 0.5 g/dl. The corresponding figures for the UV and UA bloods were 16 ± 0.6 and 15.6 ± 0.6 g/dl, respectively. No baby had an Apgar score of less than 7 at 1 minute. At 5 minutes all babies had an Apgar score of at least 9. No patient

had a mean blood pressure of less than 90 torr before delivery of the infant.

Discussion

The relation between maternal and fetal P_{O_2} had been studied by many authors. General anesthesia was used in three of these studies (1-3), and epidural anesthesia in three others (9-11). Fox and Houle (9) assessed fetal P_{O_2} at a maternal F_{IO_2} of 0.21 or 1.0. The other two studies (10, 11) were limited to a F_{IO_2} of 1.0. However, in our study a wider range of MA P_{O_2} was obtained by increasing maternal F_{IO_2} from 0.21 to 1.0 by approximately 0.26 increments. This enabled us to assess whether a critical MA P_{O_2} existed, beyond which fetal oxygenation was unaffected or adversely affected.

Our data show that fetal and maternal P_{O_2} correlated positively with each other over a maternal P_{aO_2} range of 70 to 490 torr (Fig 2). The wider scatter of UA P_{O_2} was probably due to variation in fetal oxygen consumption. UV and UA P_{O_2} neither reached a plateau nor declined at a MA P_{O_2} of greater than 300 torr. Our data are in close agreement with those of Fox et al (10) and Newman et al (12). Fox et al (10), found that a MA P_{O_2} of 326 torr produced a UV and a UA P_{O_2} of 38 and 22 torr, respectively. These are close to our fetal values of 41 and 22.4 torr. In Fig 3 our

TABLE 3

P_{CO_2}, pH, and BE_3 Values in Different F_{IO_2} Groups in Maternal Artery, Umbilical Vein, and Umbilical Artery*

Maternal F_{IO_2}	Maternal artery			Umbilical vein			Umbilical artery		
	P_{CO_2}	pH	BE_3	P_{CO_2}	pH	BE_3	P_{CO_2}	pH	BE_3
0.21	27.60 ± 1.20	7.448 ± 0.006	−5.40 ± 0.60	35.40 ± 1.10	7.37 ± 0.08	−4.50 ± 0.50	44.2 ± 1.6	7.33 ± 0.09	−2.64 ± 0.35
0.47	29.30 ± 0.80	7.480 ± 0.007	−1.90 ± 0.52	41.10 ± 0.75	7.37 ± 0.01	−1.20 ± 0.44	48.0 ± 1.2	7.33 ± 0.01	0.27 ± 0.52
0.74	29.20 ± 1.05	7.460 ± 0.006	−2.80 ± 0.70	39.00 ± 1.00	7.38 ± 0.09	−1.12 ± 0.45	48.0 ± 1.3	7.34 ± 0.07	0.09 ± 0.91
1.00	28.60 ± 0.50	7.460 ± 0.006	−3.20 ± 0.60	38.60 ± 1.30	7.39 ± 0.01	−1.93 ± 0.44	48.2 ± 0.4	7.32 ± 0.005	−0.43 ± 0.35

* Values are means ± 1 SE of data from 10 patients. *p* values are given in Table 4.

TABLE 4

p Values from Intergroup Comparison of Means of P_{CO_2}, pH, and BE_3 Values from Maternal Artery and Fetal Umbilical Vein and Artery at Different Levels of Maternal F_{IO_2}

F_{ICO_2} groups compared	Maternal artery			Umbilical vein			Umbilical artery		
	P_{CO_2}	pH	BE_3	P_{CO_2}	pH	BE_3	P_{CO_2}	pH	BE_3
0.21 vs 0.47	0	0	3	3	0	3	1	0	3
0.21 vs 0.74	0	0	2	1	0	3	1	0	2
0.21 vs 1.00	0	0	2	1	0	3	1	0	3
0.47 vs 0.74	0	0	0	0	0	0	0	0	0
0.47 vs 1.00	0	0	0	0	0	0	0	0	0
0.74 vs 1.00	0	0	0	0	0	0	0	0	0

* Numbers 1, 2, and 3 represent *p* values < 0.05, 0.01, and 0.001, respectively; zero = not significant.

TABLE 5

Anesthetic Induction to Delivery Time (ID) and Uterine Incision to Delivery Time (UD) in Four F_{IO_2} Groups*

Group	ID	UD
	min	*sec*
1	36 ± 4	64 ± 6
2	35 ± 5	68 ± 7
3	34 ± 3	72 ± 11
4	37 ± 5	69 ± 9

* Values are means ± 1 SE of data from 10 patients. There was no statistical difference between any of the means.

regression line is compared with that of Newman et al (12): fetal scalp P_{O_2} (torr) = 0.06 × MA P_{O_2} + 17.69 (12). Because fetal scalp P_{O_2} is 7 to 9 torr lower than UV P_{O_2} (12), the two regression lines can be considered nearly identical. At clinically seen fetal P_{O_2} values, the fetal oxyhemoglobin dissociation curve is nearly vertical. Small increases in fetal P_{O_2} will, therefore, significantly increase fetal oxyhemoglobin saturation and total blood oxygen content. The improved oxygen stores will enable the fetus to withstand unexpected intranatal or postnatal oxygen deprivation (2).

However, our findings differ considerably from those of three other studies which stated that fetal P_{O_2} declined (1), attained a plateau (2), or correlated poorly with MA P_{O_2} (3) when MA P_{O_2} exceeded 300 torr. Several factors may have been responsible for
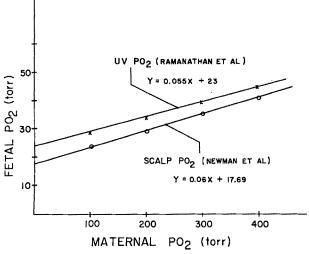
FIG 3. Regression line representing relation between values of fetal vein P_{O_2} and maternal Pa_{O_2} from our study compared with that reported by Newman et al (12) for correlation between values of maternal Pa_{O_2} and fetal scalp P_{O_2}. Regression line slopes are nearly identical. Y-intercept in our study was higher because UV P_{O_2} is usually 7 to 9 torr higher than scalp P_{O_2} (12).

the discrepancy. In these three studies, general anesthesia was used. The anesthetic technique was not standardized for different levels of F_{IO_2}. For instance, Rorke et al (1) used 66% or 33% N_2O with 2% diethyl ether for their low and high levels of F_{IO_2}, but 0.3% methoxyflurane when F_{IO_2} of 1.0 was studied. In addition, the mean ID intervals in patients who

breathed low and high levels of F_{IO_2} were 47.4 and 45.9 minutes, respectively. However, when the F_{IO_2} was 1, it was 52.3 minutes, thus prolonging fetomaternal exposure to methoxyflurane. Marx and Mateo (2) used 65% O_2 and 33% N_2O with 1.25% fluoroxene for the study of medium levels of F_{IO_2}, 6.5% cyclopropane for the 93% O_2 group, and 2.5% fluoroxene for the 97% O_2 group. In Baraka's study (3), the only three patients in the 100% O_2 group received 0.5% of halothane. However, patients given lower oxygen concentrations received varying amounts of N_2O. In all three studies, the absence of N_2O in the anesthetic mixture when F_{IO_2} was 1 necessitated the use of a potent volatile anesthetic and/or the highest concentration of that agent. Reduction in maternal and/or fetal cardiac output may have contributed to their findings.

The number of variables in our study was minimized as follows: (a) the same local anesthetic was used in all patients; (b) ID and UD intervals were similar (Table 5); (c) all patients rehearsed mask breathing before the procedure to decrease apprehension and hyperventilation; (d) even when the F_{IO_2} was 0.21, patients breathed the gas mixture from the mask and not just room air; and (e) maternal cardiac output was optimized by prophylactic hydration and maintenance of left uterine displacement throughout ID interval.

Hyperoxia shifts the CO_2 dissociation curve downward and decreases the ability of hemoglobin to transport CO_2 (Haldane effect). However, the MA P_{CO_2} in the hyperoxic patients was not significantly higher than in normoxic patients: the awake state of our patients probably enabled them to augment minute ventilation in response to an increasing P_{aCO_2}. Fox et al (10) also reported a similar finding in their study. In our study both UV and UA P_{CO_2} in the hyperoxic patients were higher than in normoxic patients. The failure of increasing fetal oxyhemoglobin saturation to elevate further P_{CO_2} levels of the hyperoxic fetuses may be due to similar blood fixed acid contents. The fetal BE_3 values were not significantly different from each other in the three hyperoxic groups (Tables 3 and 4). This might have counteracted the hyperoxia-induced downward shift of the CO_2 dissociation curve (10).

Maternal hyperoxia during cesarean sections performed under epidural anesthesia has been reported to improve fetal acid-base status (9). In our study the hyperoxic fetuses were less acidotic than normoxic babies (Table 3). Despite the improved acid-base status, the 1-minute Apgar scores were similar in all the babies. This may be due to the fact that Apgar scores are not sensitive enough to detect subtle fetal biochemical changes (13). The UV and UA pH values of all the babies in our study ranged from 7.37 to 7.39 and 7.32 to 7.34, respectively, at the time of delivery. At these fetal pH levels, the 1-minute Apgar score is unlikely to be less than seven (14). Increased metabolic cost of (pregnancy-induced) pulmonary hyperventilation and elevated basal metabolic rate (15) produce some degree of maternal acidosis. Maternal hyperoxia seems beneficial in alleviating maternal acidosis, as evidenced by smaller base deficits in hyperoxic mothers than in normoxic subjects.

The fetal ductus arteriosus is constricted by a high ductal blood P_{O_2} level both in intact animals and isolated tissue preparations (16, 17). The increase in ductal vascular smooth muscle tone is more striking at P_{O_2} levels in excess of 50 torr (16). Thus, there exists a theoretical possibility that fetal hyperoxia may cause premature closure of the ductus of the unborn fetus. However, this has not been a problem in clinical practice. Several authors have administered oxygen to mothers both during labor (12, 18, 19) and during cesarean sections (9–11) at F_{IO_2} levels ranging from 0.5 to 1. None of these authors reported any specific fetal problems attributable to premature ductal closure. All our hyperoxic babies had uneventful early neonatal and nursery courses as well. In our study, the highest values for fetal UV and UA P_{O_2} (which were 53 and 33 torr, respectively) were found in a patient who inhaled an F_{IO_2} of 1. The P_{O_2} of ductal blood is usually less than UA P_{O_2} because the ductal blood flow mainly consists of the fetal right ventricular output (20). Therefore, the ductal blood P_{O_2} may not reach (even in the hyperoxic fetuses) the critical level capable of inducing premature closure of the ductus.

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Assessment of Two Noninvasive Monitors of Arterial Oxygenation in Anesthetized Man

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The Hewlett-Packard 47201A ear oximeter and the Radiometer TCM$_t$ transcutaneous oxygen monitor were evaluated for use as noninvasive monitors of arterial oxygenation during inhalational anesthesia in man. Thirty-four healthy adult volunteers were anesthetized to steady states with halothane, enflurane, or isoflurane, and were studied either before or during surgery. Oxygen levels were varied over ranges that included hypoxemia, by manipulating FI_{O_2}. Oximeter estimates of Sa_{O_2} values and transcutaneous estimates of Pa_{O_2} values were compared with conventional measurements of each. Oximeter readings responded rapidly to changes of inspired oxygen concentration and were acceptably accurate estimates of Sa_{O_2}, except at lower Sa_{O_2} levels (<80%) during anesthesia without surgery. Transcutaneous oxygen tension readings responded relatively slowly to changes of FI_{O_2} and were frequently inaccurate reflections of Pa_{O_2} values. We consider this oximeter suitable as a monitor of arterial oxygenation during anesthesia, but find the transcutaneous electrode unsatisfactory.

MODERATE HYPOXEMIA can be difficult to detect clinically in anesthetized patients (1, 2), especially in the absence of freshly shed blood in the surgical field. Methods available for monitoring arterial oxygenation continuously and noninvasively include ear oximetry (3) and transcutaneous measurements of oxygen tension (4). The accuracy of each has been evaluated in awake volunteers over ranges of Sa_{O_2} and Pa_{O_2} values that included hypoxemia (5-9), but in anesthetized volunteers at normal and increased Sa_{O_2} and Pa_{O_2} values only (10-14). Findings cannot be extrapolated confidently from the awake state to anesthesia because anesthesia may alter the reliability of these techniques through its effects on skin perfusion, temperature, and acid-base balance.

We have evaluated a Hewlett-Packard 47201A ear oximeter and a Radiometer TCM$_I$ transcutaneous oxygen monitor as monitors of arterial oxygenation in healthy anesthetized patients both before and during surgery. Oximeter and transcutaneous P_{O_2} readings were compared with conventional measurements of Sa_{O_2} and Pa_{O_2} values over ranges of oxygen levels that included hypoxemia.

Methods

This study was approved by the University of Western Ontario Committee on Human Research and each subject gave written informed consent. Subjects were selected from healthy patients (A.S.A. class I) scheduled for elective orthopaedic or dental surgical procedures, and were divided into two groups. In Group I, we tested the ear oximeter; in Group II, the transcutaneous oxygen monitor was tested.

Each patient was studied during a steady state of inhalational anesthesia, either immediately before or during his surgical procedure. Anesthesia was induced with intravenous thiopental (5 to 7 mg/kg) or with the inhaled agents to be subsequently used for maintenance, which were halothane, enflurane, or isoflurane, with or without N_2O 50%. Vaporizer concentrations were set to achieve end-tidal concentra-

tions equivalent to 1.1 to 1.3 MAC, taking into account the MAC effect of N_2O (15). An intravenous infusion (dextrose 5% in 0.2% saline) was administered as necessary to keep systolic pressure at 70% (or greater) of awake values. Subjects breathed spontaneously throughout.

The oximeter was standardized according to the manufacturer's directions. (These include having the oximeter measure and store for reference intensities of light transmitted through the ear probe gap while it is open and then with an analogue inserted.) The superior portion of the subject's pinna was arterialized with a nicotinic acid containing rubefacient (Finalgon) and the heated oximeter probe (41.5°C) was positioned over the antihelix. The response of the instrument was set at "N" (normal). A 5 minute period was allowed for stabilization.

The transcutaneous oxygen electrode was heated to 44°C and then calibrated in tonometers containing 0% and 21% oxygen. The electrode assembly was applied to the anterior chest wall just below a clavicle, using the manufacturer-supplied electrode ring and contact gel. A period of 20 minutes was allowed for stabilization. After each study, the electrode was recalibrated in vitro to determine the magnitude of sensor drift.

We wished to vary oxygen levels during reasonably steady anesthetic and respiratory states. Accordingly, we allowed at least 30 minutes for anesthetic equilibration and in studies conducted during surgery, we avoided periods of potent surgical stimuli. Arterial oxygenation was varied by manipulating the nitrogen concentration of inspired gas in a manner that would produce several levels of steady end-tidal oxygen concentration between 20% and 6.5%. Airway concentrations of oxygen, carbon dioxide, nitrous oxide, and anesthetic vapor were monitored continuously with a calibrated Perkin-Elmer #1100 mass spectrometer. Outputs of the mass spectrometer, together with the output of the instrument being tested, were inscribed continuously on a multichannel recorder.

After the oximeter or the electrode reading had stabilized at each end-tidal oxygen concentration (percent or torr readings ± 1 for 20 seconds), a sample of blood was drawn from an indwelling catheter, which had been placed in a radial or dorsalis pedis artery, for subsequent blood gas analysis. The sample was capped and placed in ice immediately, and was analyzed within the hour with a calibrated Radiometer Copenhagen BMS 3 system. P_{O_2} values were corrected for membrane, halothane, and memory effects. Saturations were computed with a Severinghaus blood gas

calculator (BGC I), assuming each subject's P_{50} was 26.6. torr (16).

We compared mean oximeter and mean transcutaneous P_{O_2} readings, observed during periods of blood sampling, to calculated Sa_{O_2} and measured Pa_{O_2} values, respectively. For each comparison, we computed the least-squares linear regression, the SD from regression and the 95% confidence limits (17). In addition, errors in the estimates of Sa_{O_2} and Pa_{O_2} values were determined for subdivisions of the ranges of values studied.

Results

There were 34 subjects, 19 men and 15 women, whose ages heights and weights (mean ± SD) were, respectively, 30 ± 9 years, 171 ± 9 cm, and 71 ± 15 kg. Clinical characteristics of each group are shown in Table 1. Within each group, approximately half the subjects received halothane, the remainder either enflurane or isoflurane. Two to eight arterial oxygen levels were studied in each subject.

The in vivo response of the oximeter to changes in inspired oxygen was always rapid and in the appropriate direction. Giving 100% oxygen to hypoxemic subjects caused oximeter readings, after a delay of approximately 5 seconds, to increase exponentially to a new steady level with a mean time constant of 6.6 ± 0.7 (SD) seconds.

At normal levels of arterial saturation (Sa_{O_2}, 90%+),

TABLE 1

Clinical Variables*

	Group I ear oximeter	Group II transcutaneous oxygen monitor
No. of patients		
Anesthesia	7	7
Anesthesia and surgery	7	13
Hemoglobin (g%)†	14.7 ± 1.3	15.2 ± 1.5
Temperature (°C)†‡	36.0 ± 0.3	36.3 ± 0.5
Systolic blood pressure (torr)		
Anesthesia	101 ± 10	102 ± 7
Anesthesia and surgery	116 ± 12	116 ± 11
pH		
Anesthesia	7.30 ± 0.03	7.30 ± 0.04
Anesthesia and surgery	7.33 ± 0.05	7.33 ± 0.05
Pa_{CO_2} (torr)		
Anesthesia	50 ± 8	51 ± 6
Anesthesia and Surgery	43 ± 7	44 ± 9

* Values are means ± SD.

† Hemoglobin and temperature values are similar for both anesthesia and anesthesia and surgery groups.

‡ Nasopharyngeal temperature.

steady oximeter readings agreed closely with calculated values of Sao_2; during hypoxemia (Sao_2, 70% to 89%), readings tended to overestimate Sao_2 values slightly (Table 2; Fig 1, $y = 0.83x + 15.6$, $n = 94$, $r = 0.95$, SD from regression $= 2.5$). Readings were more accurate during anesthesia with surgery ($y = 0.91x + 8.9$, $n = 52$, $r = 0.97$, SD from regression $= 1.8$) than during anesthesia alone ($y = 0.77x + 22.6$, $n = 42$, $r = 0.93$, SD from regression $= 3.1$) (p value for difference between slopes <0.05).

The in vivo response of the transcutaneous electrode to a step change in Fio_2 values was extremely variable and relatively slow. Readings occasionally took as long as 15 minutes to stabilize completely.

Stable transcutaneous Po_2 values varied considerably at all levels of Pao_2 (Table 3; Fig 2, $y = 0.73x + 14.4$, $n = 44$, $r = 0.68$, SD from regression $= 19.7$). There were two errors in detecting the direction of small (<8 torr) Pao_2 changes—transcutaneous Po_2 val-

TABLE 2

Accuracy of Ear Oximeter

Range of Sao_2	No. of observations	Errors in estimate of Sao_2*	
		Mean ± SD	Maximum
%			
90+	46	−0.2 ± 1.7	−4.0
80–89	32	1.1 ± 2.5	+6.0
70–79	16	3.3 ± 2.7	+9.5

* Oximeter measurements (%) less calculated Sao_2 (%).
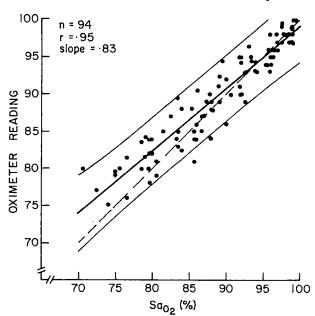
FIG 1. Comparison of oximeter readings and calculated Sao_2 values. Heavy continuous line is line of regression. Lighter continuous lines represent 95% confidence limits. Dashed line is line of identity.

TABLE 3

Accuracy of Transcutaneous Oxygen Monitor

Range of Pao_2	No. of observations	Errors in estimate of Pao_2*	
		Mean ± SD	Maximum
torr			
100+	12	−22 ± 16	−46
70–99	20	−3 ± 16	−37
40–69	12	−3 ± 14	−24

* Transcutaneous Po_2 (torr) less Pao_2 (torr).
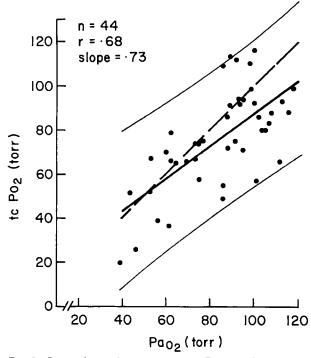
FIG 2. Comparison of transcutaneous Po_2 and Pao_2 values. Heavy continuous line is line of regression. Lighter continuous lines represent 95% confidence limits. Dashed line is line of identity.

ues increased when Pao_2 values decreased—both during enflurane anesthesia. There was no detectable difference between findings during anesthesia alone and during anesthesia with surgery, and no detectable difference among findings with halothane, isoflurane or enflurane.

Drift of the transcutaneous electrode at the 21% oxygen calibration point was positive in 10 subjects zero in six, and negative in four. Overall mean drif was +1 ± 3 (SD) torr/hr over study periods of 40 t 150 minutes. The zero calibration point was stabl throughout.

Discussion

There are several limitations to the potential accu racy of each of these monitoring techniques. The ea

oximeter estimates the proportion of oxygenated hemoglobin in arterial blood from the transmission of red light through a region of the heated and arterialized pinna. However, several variables other than hemoglobin saturation may influence this transmission, including skin thickness, other light absorbing pigments, local tissue inhomogeneity, and local blood flow (3). The transcutaneous oxygen monitor estimates arterial Po_2 values by measuring the oxygen tension at the surface of a region of heated and arterialized skin, using a Clark-type electrode with a membrane designed to limit the Po_2 gradient between capillary blood and the membrane surface (4). Variables that influence the transcutaneous Po_2 estimate of Pao_2 values include the temperature effect on local blood Po_2, oxygen consumption of local tissues, and resistance of the skin to O_2 diffusion (18). In addition, the accuracy of both methods depends on the adequacy of heat-induced arterialization of dermal capillaries.

These theoretical limitations notwithstanding, the recently developed HP ear oximeter and several transcutaneous monitors have been reported to approximate closely actual Sao_2 and Pao_2 values in normal awake man (5–8). The HP oximeter is considered to have minimized the influence of variables other than hemoglobin saturation by measuring light transmittance at eight wavelengths (in contrast to the conventional two) and computing saturations on the basis of these values and certain constants that have been found to relate best transmittance values to actual saturations in a diverse group of volunteers (19). Transcutaneous Po_2 monitors have been found to be particularly reliable in newborn infants (4).

In our anesthetized subjects, the HP oximeter predicted normal Sao_2 values adequately and followed changes of Sao_2 rapidly and correctly. It tended to overestimate the lowest Sao_2 values, particularly in subjects tested during anesthesia alone. The basis for this overestimation during anesthesia—which was not as evident during anesthesia with surgery nor in the awake state (5, 6)—is not clear. Perhaps the reduced arterial blood pressure during anesthesia acted to reduce perfusion of the pinna, an effect that could alter the oximeter's performance especially at lower saturations (3). In any case, falsely high Sao_2 values were consistent only at saturations less than 80%—i.e., saturations not commonly encountered in clinical practice.

Overall, our study may have underestimated the accuracy of the ear oximeter, as we did not measure saturation directly but calculated it on the basis of

measured Pao_2, assuming one value of P_{50} for all subjects and single constants for the effects of pH and base excess (16). We did not consider possible interfering effects of carboxyhemoglobin, which in concentrations greater than 9% may falsely increase the readings of this oximeter (20). However, there were no heavy smokers among our subjects.

The transcutaneous Po_2 electrode, when used in awake adults, is usually heated to 45°C, a temperature chosen to maximize arterialization without producing an undue risk of burns. However, in one of our first uses of the electrode in anesthetized subjects, 45°C caused blisters at the monitoring site. We subsequently set the electrode at 44°C and have had no further incidents of burn.

In agreement with previous findings in intensive care and postoperative patients (9), the response of the transcutaneous Po_2 electrode to a change in Fio_2 was relatively slow. In keeping with other observations in anesthetized adults (12–14), the instrument's accuracy in predicting normal Pao_2 values was poor. Reliability at reduced oxygen tensions was also unsatisfactory. It has been suggested that even when inaccurate in estimating absolute Pao_2, the transcutaneous Po_2 electrode may be useful in following Pao_2 trends, because of reasonably constant transcutaneous Po_2/Pao_2 ratios within individuals (7, 8, 13). However, even trend detection was not consistently correct in this study. Overall, we consider this particular system inadequate as a monitor of arterial oxygenation in anesthetized adults.

The poor performance of the transcutaneous Po_2 electrode was no doubt due to limitations inherent in this technique (18), perhaps complicated during anesthesia by factors such as hypothermia, hypotension, and acidemia, which in themselves can alter transcutaneous estimates of Pao_2 (9, 12, 21). We cannot attribute poor performance to halothane diffusing through the heated skin (12), as the accuracy of readings during halothane anesthesia was not significantly different from that found during isoflurane or enflurane anesthesia.

We conclude that the Hewlett-Packard ear oximeter is suitable as a noninvasive and continuous monitor of arterial oxygenation in healthy anesthetized man. In addition to being reasonably accurate, it was stable, rapidly responsive, and relatively easy to standardize and use. It should be noted that the accuracy observed in normal healthy subjects may not necessarily apply in all conditions. Oximeter estimates may be falsely low in the presence of an elevated bilirubin, falsely high in the presence of carboxyhemoglobin, and un-

reliable in patients with anemia, hypothermia, or any condition that reduces perfusion of the pinna (3, 19, 20).

ACKNOWLEDGMENTS

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Pharmacokinetics of Inhalation Anesthetics: A Three-Compartment Linear Model

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The evolution of mathematical models of the uptake of the inhaled anesthetic agents has produced increasingly complex models in which researchers have attempted to incorporate more and more data on the effects of anesthetics on the processes of respiration, circulation, and metabolism. One result of this evolution has been to limit the application of these models due to the large amount of data required by the model and the need for a large digital computer to generate a solution. The purpose of this study is to show that a three-compartment linear model, using only the solubility of an anesthetic in water and oil, may be used to predict the uptake of a volatile anesthetic with sufficient accuracy for practical purposes. Only a programmable hand calculator is needed for the solution. Due to the simplicity of this model, compared with previously described models, it should prove useful in understanding the kinetics of gas uptake by the body.

NUMEROUS physiologically based pharmacokinetic models have been proposed to describe the uptake of inhaled anesthetics (1-7). These models are all flow-limited models. They assume that the rate of an anesthetic's uptake is limited only by the rate at which it arrives at the tissues. One of the earliest models, the two-compartment model of Kety (1), provided a gross estimate of the alveolar-to-inspired concentration ratio based only on the solubility of the agent in blood, body weight (or volume), alveolar minute ventilation, and cardiac output. Kety's model can be solved exactly (i.e., it is precisely defined by an equation). Given the required data, a solution can be obtained in approximately 4 minutes with a pocket calculator such as the Texas Instruments TI-35 or Sharp EL-5813 (Appendix).

Subsequent models have sought to obtain a better correlation with observed data by dividing the body into tissue groups according to their blood flows. Four or more tissue groups or compartments have usually been used. Both linear and nonlinear models have been proposed. The nonlinear models attempt to incorporate the concentration effect, second gas effect, and anesthetic-induced changes in ventilation, cardiac output, and regional blood flow. In contrast to Kety's model, these models depend on the measurement of blood and tissue solubilities of the anesthetic. A digital, analog, or hybrid computer is needed to solve such models due to the number of compartments and the nonlinear kinetics. The solutions to all of the models subsequent to Kety's are approximate in that they are expressed in the form of a graph or table, rather than by an exact equation. ("Approximate" in this context does not imply "inaccurate." In fact, the approximation can usually be made to almost any desired degree of accuracy, with a digital computer, given sufficient processing time.)

In reviewing some of the previously published models, several problems are evident. One problem is the dependence on the measurement of the blood and tissue solubilities of the anesthetic. For a new anesthetic, these data may not be available. Even for the older agents, there is variation among the data reported by different investigators. For instance, the reported muscle/gas partition coefficients for halothane range from 2.92 to 8.0 (8). Another problem is the lack of standards regarding the symbols used by different authors, and regarding the form of mass transfer equations. The lack of standard terminology makes comparison between models particularly difficult. For instance, Kety solved for the concentration

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of the inert gas in the lung (1). Eger (2) and Mapleson (3), in their original models, solved for the volume of the anesthetic in the lung and tissue compartments. Subsequent models have solved for the partial pressure of the anesthetic (4, 6). Also, the computational requirements of a large model may cause problems for some investigators due to the limited availability of large computers. The eight-bit microcomputers currently available can solve these models, but the computational time may be inconveniently long.

The purpose of this study was to determine whether a three-compartment linear model based on the solubility of an anesthetic in water and oil, and using other reasonable assumptions and approximations, could predict the alveolar-to-inspired concentration ratio with sufficient accuracy to be useful. The rationale for basing the model on the solubility of the anesthetic in water and oil is based on the premises that (a) the body consists mostly of water and lipids, and (b) inhalational anesthetics are not bound to proteins. A three-compartment linear model is about the most complicated that can practically be solved exactly with a programmable hand-held calculator such as the Texas Instrument TI-59.

Methods

A three-compartment linear model was constructed to predict the alveolar-to-inspired concentration ratio of an anesthetic, and hence the anesthetic uptake. The model consists of a central compartment and two peripheral compartments, one "fast" and one "slow."

The model makes several assumptions. First, it assumes a 70-kg subject with a cardiac output of 5 L/min and an alveolar minute ventilation of 4 L/min. Cardiac output and alveolar ventilation are assumed to remain constant. It also assumes that the inflow of anesthesia is constant and that the rate of transfer between compartments is linearly related to anesthetic partial pressure gradients. The mass-transfer equations are written to conform with conventional pharmacokinetic models.

The model is illustrated in Fig 1. The central compartment represents lung gas, pulmonary venous blood, and arterial blood. The volume of lung gas 2.3 L. The volume of blood in this compartment is assumed to be 1 L.

The fast peripheral compartment consists of 9% of the body volume and receives 75% of the cardiac output. This is analogous to Eger's vessel-rich group (2) and Mapleson's visceral compartment (3). The slow peripheral compartment consists of 50% of the (functional residual capacity [FRC]) is assumed to be body volume and receives 18% of the cardiac output. This corresponds to the muscle group of both Eger (2) and Mapleson (3). The transfer of anesthetic between central and peripheral compartments is assumed to be instantaneous. Thus, this model does not consider circulation time. (Mapleson (9) has discussed the theoretical implications of circulation time and the distribution of venous blood on models of anesthetic uptake. These factors lead to small differences in the predicted results.)

As alluded to earlier, the model predicts an anesthetic's solubility in blood and tissue from its Oswald solubility coefficient in water and oil. For this prediction, blood is assumed to consist of 99.1% water and 0.9% oil, (i.e., lipid). The ability of this arbitrary formula to predict the blood/gas partition coefficient of an anesthetic agent is shown in Table 1. The

ABBREVIATIONS

Fi	inspired concentration
Fa	alveolar concentration
k_{ij}	rate of transfer of drug from compartment i to compartment j
M_i	mass of drug in compartment i
M_i'	dM_i/dt
M_i''	d^2M_i/dt^2
M_i'''	d^3M_i/dt^3
S_w	water/gas solubility coefficient
S_{oil}	oil/gas solubility coefficient
$\lambda B/G$	blood/gas partition coefficient
$\lambda T_2/B$	tissue/blood partition coefficient for second compartment
$\lambda T_3/B$	tissue/blood partition coefficient for third compartment
CO	cardiac output (5 L/min used)
V_a	alveolar minute ventilation (4 L/min used)
FRC	functional residual capacity (2.3 L used)
V_i	volume of compartment i
r_1, r_2, r_3	roots of characteristic equation
f/d	particular solution (solution to forcing function)
U(t)	whole body uptake of anesthetic agent (ml vapor)
e	base of natural logarithms (2.718 …)

FIG 1. Schematic representation of three-compartment model of anesthetic uptake.

TABLE 1

**Predicted and Measured Values for Blood/Gas (BG)
Partition Coefficient for 16 Anesthetics***

Anesthetic	BG predicted	BG measured	Percent error
Chloroform	7.56	8.00	5.8
Cyclopropane	0.31	0.55	77.0
Diethyl ether	13.50	12.00	11.0
Divinyl ether	1.90	2.60	37.0
Enflurane	1.65	1.90	15.0
Ethylene	0.10	0.15	50.0
Fluroxene	1.27	1.40	10.0
Isoflurane	1.49	1.40	6.0
Halothane	2.77	2.40	13.0
Krypton	0.054	0.06	11.0
Methoxyflurane	13.0	11.00	15.0
Nitrogen	0.014	0.015	7.0
N_2O	0.48	0.47	2.0
Teflurane	0.58	0.60	3.0
Trichloroethylene	9.80	9.00	8.0
Xenon	0.10	0.14	40.0

* Measured values are those compiled by Steward et al (8).

correlation between the predicted and observed values is $r = 0.99$ ($p = 0.013$).

For the prediction of the tissue/blood partition coefficients, the fast peripheral compartment is assumed to consist of 98% water and 2% oil; the slow peripheral compartment is assumed to consist of 97% water and 3% oil. Thus, the equations for the solubility coefficients are:

$$\lambda B/G \text{ (predicted)} = 0.991\, S_w + 0.009\, S_{oil}$$

$$\lambda T_2/B \text{ (predicted)} = \frac{0.98\, S_w + 0.02\, S_{oil}}{\lambda B/G}$$

$$\lambda T_3/B \text{ (predicted)} = \frac{0.97\, S_w + 0.03\, S_{oil}}{\lambda B/G}$$

Turning now to the kinetics of uptake and distribution in the model, the differential rate equations that describe the system are:

$$M_1' = k_{01} + k_{21}M_2 + k_{31}\, M_3 - (k_{10} + k_{12} + k_{13})\, M_1 \quad (1)$$

$$M_2' = k_{12}M_1 - k_{21}M_2 \quad (2)$$

$$M_3' = k_{13}M_1 - k_{31}M_3 \quad (3)$$

Here, M_i is the mass of drug in compartment i, and M_i' is the first derivative (rate of change) of the mass in compartment i.

The six rate constants (k_{01}, k_{21}, etc) are the heart of the model. The exact definitions of each are defined below. Using these definitions, for instance, one could easily modify the model to correspond to different assumptions as to cardiac output, ventilation, compartment volumes, etc.

k_{01} (rate of input to the central compartment) is so defined that the mass of anesthetic in that compartment is always equal to the alveolar-to-inspired concentration ratio. Thus, if there was no anesthetic uptake by peripheral compartments, the anesthetic mass in the central compartment would start at 0 and rise, eventually, to 1. This has the advantage that after solution of the equations, no further conversion is required to obtain the alveolar-to-inspired concentration ratio. This requires that:

$$k_{01} = V_a/V_1$$

$$V_1 = (FRC + 1 \times \lambda B/G)$$

where V_a is alveolar minute ventilation, V_1 is the volume of the central compartment, and FRC is the functional residual capacity.

The rate of loss from the central compartment is $k_{10}M_1$, where k_{10} is set equal to k_{01} plus an additional term representing the loss of anesthetic to tissues with especially long time constants, such as fat, and to metabolism. Seven percent of the cardiac output is assumed to go to these tissues and the anesthetic delivered to these tissues is considered to be irreversibly lost. This approximation makes the model more realistic without adding additional compartments. Justification for this approximation can be found in the data of Fiserova-Bergerova and Holaday (10) who found significant uptake of anesthetic after 2 hours of administration. Recent studies by Morgan et al (11) on the kinetics of thiopental also suggest that over the period of a typical anesthetic administration, distribution of thiopental to tissues with especially long time constants may mimic excretion or irreversible loss. Thus:

$$k_{10} = k_{01} + \frac{0.07 \times CO \times \lambda B/G}{V_1}$$

where CO is the cardiac output.

The rate of transfer of anesthetics from the central compartment into the second compartment is $k_{12}M_1$, where:

$$k_{12} = \frac{0.75 \times CO \times \lambda B/G}{V_1}$$

The rate of transfer of anesthetics from the second compartment back into the central compartment is $k_{21}M_2$, where:

$$k_{21} = \frac{0.75 \times CO}{V_2 \times \lambda T_2/B}$$

The rate of transfer of anesthetic from the central compartment to the third compartment is $k_{13}M_1$, where:

$$k_{13} = \frac{0.18 \times CO \times \lambda B/G}{V_1}$$

The rate of transfer of anesthetics from the third compartment back into the central compartment is $k_{31}M_3$, where:

$$k_{31} = \frac{0.18 \times CO}{V_3 \times \lambda T_3/B}$$

There is no specific representation of the venous blood. The venous blood is considered to be part of each tissue compartment and has the same anesthetic concentration as the tissue that it drains.

Thus, three simultaneous first order differential equations are obtained (equations 1 to 3). To solve these, they must be combined as shown in equation 4, to obtain a third order equation containing M_1 and its derivatives:

$$M_1''' + bM_1'' + cM_1' + dM_1 = f \qquad (4)$$

Here, the constants b, c, d, and f are related to the rate constants as follows:

$$b = k_{10} + k_{12} + k_{13} + k_{21} + k_{31}$$

$$c = k_{31}(k_{10} + k_{12} + k_{21}) + k_{21}(k_{10} + k_{13})$$

$$d = k_{31}(k_{13}(k_{31} - k_{21}) + k_{21}(k_{10} + k_{13}) - k_{31}k_{13})$$

$$f = k_{31}\,k_{21}\,k_{01}.$$

To solve equation 4, one must solve the homogeneous equation:

$$M_1''' + bM_1'' + cM_1' + dM_1 = 0 \qquad (5)$$

The solution of this homogenous third order linear differential equation is:

$$y(t) = Ae^{r_1 t} + Be^{r_2 t} + Ce^{r_3 t} \qquad (6)$$

where r_1, r_2, and r_3 are the roots to the characteristic equation

$$r^3 + br^2 + cr + d = 0$$

and the constants A, B, and C are determined by the initial conditions.

The complete solution is the solution of the homogeneous equation plus the particular solution:

$$M_1(t) = \frac{f}{d}$$

Thus, the complete solution is:

$$M_1(t) = \frac{f}{d} + Ae^{r_1 t} + Be^{r_2 t} + Ce^{r_3 t} \qquad (7)$$

For illustrative purposes, this solution was applied to six inhalational anesthetics: N_2O, isoflurane, enflurane, halothane, diethyl ether, and chloroform. The water and oil solubility coefficients were taken from the "preferred values" compiled by Steward et al (8). The roots of the characteristic equation were found using an iterative program with an error of 1×10^{-6} (Program MC-08 of the Texas Instruments, TI-59 Master Library).

The constants A, B, and C were found by matrix inversion (Program MC-02 of the Texas Instruments, TI-59 Master Library) given the initial conditions:

$$M_1(o) = O$$

$$M_1'(o) = k_{01}$$

$$M_1''(o) = -(k_{12} + k_{10} + k_{13})k_{01}$$

In summary then, the solution for these six agents is:

$$Fa/Fi = \frac{f}{d} + Ae^{r_1 t} + Be^{r_2 t} + Ce^{r_3 t}$$

This, then, is the three-compartment model's exact solution. Notice that this equation involves seven constants: f/d, A, B, C, r_1, r_2, and r_3. These constants need only be computed once for each anesthetic. The computed values of these constants for each of the six anesthetics are shown in Table 2.

Using the appropriate constants for the anesthetic agent being used, the value of Fa/Fi at a given time, t, can be obtained using a calculator by entering these various values (which takes less than 1 minute) and having the calculator perform the arithmetic (which takes 1 second or less).

Thus, for instance, to determine Fa/Fi at time, t = 60 minutes, for halothane (see Table 2, line 4), the following equation is evaluated:

$$Fa/Fi = .804 - 0.201e^{(-3.72 \times 60)} - 0.316e^{(-0.129 \times 60)} - 0.287e^{(-0.006 \times 60)}$$

If a programmable calculator is used, and these constants are included as part of the program, then only the time, t, must be entered manually, and the corresponding Fa/Fi is obtained virtually instantaneously.

If a new anesthetic is encountered and its solubility in oil and in water is known, then the value of those seven constants can be computed as outlined previously, and can, therefore, be incorporated directly into this exact solution.

Results

The predicted alveolar-to-inspired concentration ratio for each of the six anesthetics is shown in Fig 2. The correlation between the predicted and observed values for the six agents is shown in Figs 3 to 8. As can be seen, there is a good correlation between the predicted and observed values.

TABLE 2

Computed Values for Seven Constants in Exact Solution for Six Anesthetics*

	f/d	A	r_1	B	r_2	C	r_3
N_2O	0.960	−0.522	−2.50	−0.343	−0.388	−0.055	−0.022
Isoflurane	0.885	−0.310	−3.20	−0.361	−0.170	−0.214	−0.008
Enflurane	0.874	−0.289	−3.42	−0.357	−0.170	−0.228	−0.009
Halothane	0.804	−0.201	−3.72	−0.316	−0.129	−0.287	−0.006
Ether	0.456	−0.047	−4.95	−0.119	−0.164	−0.290	−0.009
Chloroform	0.458	−0.075	−4.95	−0.209	−0.164	−0.174	−0.009

* $Fa/Fi = (f/d) + Ae^{r_1} + Be^{r_2} + Ce^{r_3}$.
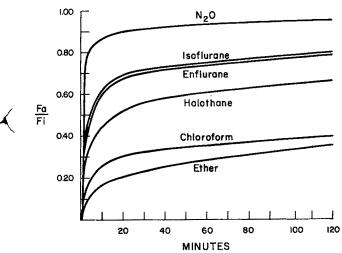
FIG 2. Predicted alveolar-to-inspired concentration ratio for six anesthetics modeled.
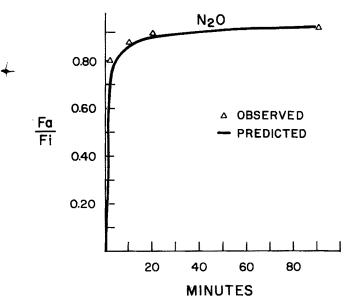
FIG 3. Comparison of predicted (solid line) and observed alveolar-to-inspired concentration ratio for N_2O. Observed data are adapted from Severinghaus (12).
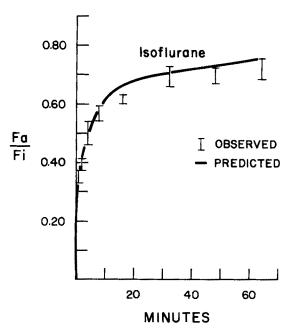
FIG 4. Comparison of predicted (solid line) and observed alveolar-to-inspired concentration ratio for isoflurane. Observed data are from Cromwell et al (13).

Discussion

The model presented in this paper has several interesting features compared with previously published models. First, it demonstrates that the pharmacokinetics of inhalation anesthetics may be approached in the same way as the pharmacokinetics of intravenous drugs, as it uses the familiar rate-constant formalism. The model also suggests that precise measurement of the blood and tissue solubilities of an anesthetic may not be a prerequisite to the prediction of its uptake.

Perhaps the greatest advantage of this model is that an exact solution may be obtained with a programmable hand-held calculator (TI-59, Texas Instruments). The computation of the seven constants for one anesthetic may be obtained in approximately 15 min-
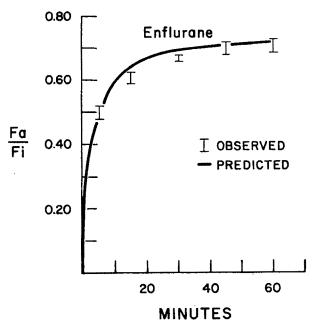
FIG 5. Comparison of predicted (solid line) and observed alveolar-to-inspired concentration ratio for enflurane. Observed data are from Torri et al (14).
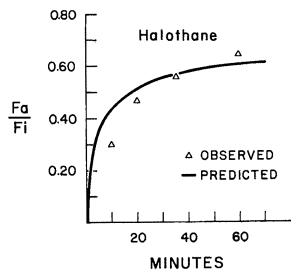
FIG 6. Comparison of predicted (solid line) and observed alveolar-to-inspired concentration ratio for halothane. Observed data are adapted from Mapleson (15).

FIG 7. Comparison of predicted (solid line) and observed alveolar-to-inspired concentration ratio for chloroform. Observed data are from Poobalasingham and Payne (16).
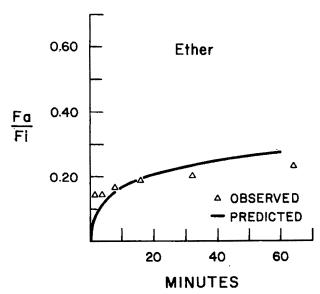
FIG 8. Comparison of predicted (solid line) and observed alveolar-to-inspired concentration ratio for ether. Observed data are from Wahrenbrock et al (17).

utes. Kety's two-compartment model (1) also is easily solved, although the predictions of Kety's two-compartment model do not correlate with the observed uptake as well the predictions of this model. A comparison between the predictions of Kety's two-compartment model and this model and the observed data for enflurane are shown in Fig 9.

The model also suggests a new algorithm for the prediction of anesthetic uptake which could be incor-

porated in an automated closed-circuit system. Here, the rate of whole body uptake of an anesthetic would be:

$$U(t) = V_a (Fi - Fa)$$

Using the model, after 20 minutes of anesthesia when the terms $Ae^{r_1 t} + Be^{r_2 t}$ become negligible, this equation could be approximated by:

$$U(t) = V_a \times Fi \times (1 - \frac{f}{d} - Ce^{r_3})$$

For example, for an inspired concentration of 1% halothane and an alveolar minute ventilation of 1 L/min, this would yield $11e^{-0.006t} + 7.9$ ml/min.
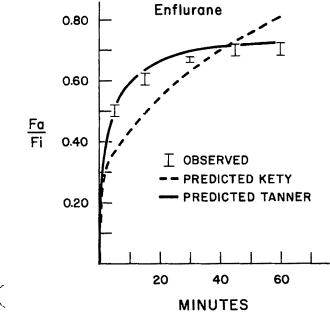
FIG 9. Comparison of predictions of Kety's two-compartment model (1) and three-compartment model presented here and observed data for enflurane. Observed data are from Torri et al (14).

Although the model presented in this paper gives good predictions of the alveolar-to-inspired concentration ratio for the anesthetics commonly used today, it does have certain limitations: (a) The concentration and second gas-effect are not accounted for. These effects, however, are small and evident only during the first few minutes of the induction of and recovery from anesthesia (18). (b) There are no circulatory shunts. The introduction of circulatory shunts into the model would add additional compartments and make an exact solution more difficult. (c) The minute ventilation and cardiac output remain constant. The introduction of anesthetically induced changes in cardiac output and alveolar minute ventilation into the model would require nonlinear kinetics and make an exact solution impossible. A slightly lower than normal value for cardiac output is used (5 L/min) to compensate for the decrease in cardiac output caused by most anesthetics. Ventilation is assumed to be either unaffected or artificially assisted to maintain a constant normal minute ventilation. (d) The model assumes that fat has an infinite capacity for anesthetic uptake. Thus, the Fa/Fi predicted by the model would, in theory, be low after a prolonged period of anesthesia.

One could expand upon the model outlined in equations 1 to 3, by adding additional compartments and adding nonlinear kinetics. One could then obtain

an approximate solution by rectangular integration of the simultaneous rate equations. Here, however, a printer for the programmable calculator would be needed, and a long computation time would be required.

In conclusion, a pharmacokinetic model of uptake of volatile anesthetics that offers an exact solution to the alveolar-to-inspired concentration ratio based on the solubility of an anesthetic in water and oil is described. The predictions of this model agree well with the observed data. The model, therefore, also suggests a new algorithm which could easily be incorporated in an automated anesthesia system.

ACKNOWLEDGMENTS

Appendix

The solution to Kety's two-compartment model is:

$$Ca/Ci = 1 - A_1 e^{-k_1 t} - A_2 e^{-k_2 t}$$

where $k_1 = \frac{1}{2}(B + \sqrt{B^2 - 4C})$, $k_2 = \frac{1}{2}(B - \sqrt{B^2 - 4C})$, $B = (V_a \times \lambda B/G \times CO)/FRC + CO/V_t$, $C = (V_a \times CO)/(FRC \times V_t)$, $A_1 = (V_a/FRC - k_2)/(k_1 - k_2)$, and $A_2 = 1 - A_1$.

V_t is the total body volume, 70 L. Kety uses 3 L as the FRC. These equations are adapted from Kety's equation 55 (1).

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REVIEW
article

Cimetidine and Related Drugs in Anesthesia

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VOMITING and regurgitation with subsequent aspiration of gastric contents into the tracheobronchial tree is an important cause of morbidity and mortality in patients undergoing anesthesia (1-4). Silent regurgitation of gastric contents is more frequent than is often appreciated, having been reported by various investigators as occurring in from 4% to 26.3% of patients having general anesthesia (5-8). As many as 76% of patients with silent regurgitation have tracheal aspiration (5). In a report on 1000 deaths associated with anesthesia in the United Kingdom, Edwards and co-workers (9) found that 18% were directly related to vomiting and regurgitation; more than 50% of all obstetric anesthetic deaths were due to aspiration of vomitus. Merill and Hingson (1) estimated that there were 100 maternal deaths from aspirations each year in the United States, whereas Phillips et al (3) estimated an average of one maternal aspiration death per year in a community of 1 million American people. Fetterman and Moran (10) concluded from autopsies that many cases of bronchopneumonia in debilitated patients and patients in coma may be attributed to aspiration of gastric contents during induction or maintenance of anesthesia with a morbidity and mortality that may reach 70% (6, 9, 11). Mendelson (12) and Teabeaut (13) demonstrated the importance of pH in the etiology of acid

aspiration. A pH of less than 2.5 is generally considered as the critical level for the development of pulmonary damage (13, 14). The risk of serious pulmonary reaction increases progressively as the pH of aspirate decreases to less than 2.5. A critical volume of acid aspirate is also necessary for widespread pulmonary damage to occur. The volume of gastric contents of pH less than 2.5 required to produce the acid aspiration syndrome has not been defined in man. The critical volume in rhesus monkeys has been shown to be 0.4 ml/kg of body weight (15). Several investigators (15-17) have suggested that patients are at risk of serious pulmonary complications with aspiration of at least 25 ml of gastric fluid with a pH of 2.5 or less.

Taylor and Pryse-Davies (18) demonstrated that 55% of obstetric patients at term have more than 40 ml of liquid gastric juice and in 42% of patients the pH is less than 2.5. Vaughan et al (19) reported that 88% of morbidly obese patients have gastric contents with a pH less than 2.5, whereas 86% had more than 25 ml of liquid gastric juice. Ong and co-workers (20) found that in outpatients receiving general anesthesia the mean gastric volume was 69 ± 17 ml with an average gastric pH of 1.8 ± 0.2; four of 21 patients had more than 75 ml of gastric fluid with pH less than 2.0. Hester and Heath (21), in their study of gastric volume and pH in emergency patients without premedication, found that in 46% of the patients the pH was less than 2.5 and in 32% of the patients the gastric volume was more than 40 ml, with maximum volumes reaching as high as 330 ml. The frequency of low gastric pH in nonobese, adult, inpatient, elective surgical patients before tracheal intubation varies from 60% to 80% (16, 22-32). Salem et al (33) and Goudsouzian and co-workers (34) found that 100% of pe-

diatric patients undergoing elective surgery had gastric pH less than 2.5.

Considering the evidence reported in the above studies, the potential risk of vomiting, regurgitation, and subsequent aspiration becomes worrisome, especially when one considers the number of patients who receive potent anesthetics by face mask without rapid sequence induction and tracheal intubation.

Reduction of Gastric Acidity

Various methods of increasing the pH of gastric contents toward neutral before the induction of anesthesia have been reported. Anticholinergic agents, oral antacids, and cimetidine have been used for this purpose, all with variable success.

Anticholinergic agents inhibit the production of gastric juice, but only to a highly variable degree. They also have side effects which include tachycardia, reduction of gastric sphincter tone, and delayed gastric emptying (35). Baraka and associates (17), in studying the effects of glycopyrrolate before cesarean section, found that gastric pH was greater than 2.5 in 66% of cases following glycopyrrolate, whereas atropine had no significant effect on gastric pH. Salem and others (33) found that in 58.1% of children premedicated with glycopyrrolate, gastric pH was greater than 2.5. The above results are promising, but in two recent studies (16, 25) glycopyrrolate failed to change significantly either the volume or pH of gastric contents compared with values in control patients, even though glycopyrrolate is generally regarded as the anticholinergic with the most pronounced effects on decreasing gastric secretions and increasing gastric pH (17, 33).

Routine antacid prophylaxis has become an established practice in obstetric anesthesia (18, 21). Roberts and Shirley (15) demonstrated that antacid administration within 4 hours of induction of anesthesia increased gastric pH to greater than 2.5 in 84% of patients, whereas only 45% of control patients who did not receive an antacid had gastric pH values greater than 2.5. However, oral antacids may also be associated with an increase in gastric volume (16, 29, 36). In addition, aspiration of antacid neutralized gastric contents even with pH greater than 2.5 may itself cause significant pulmonary damage (37–39).

Histamine has a major role in hydrochloric acid production by the parietal cells in the stomach, an effect mediated by histamine-2 (H_2) receptors (40). The discovery and introduction of H_2-receptor blocking drugs has provided a new therapeutic approach to the treatment of gastric hypersecretory states. Cimet-

idine is an H_2-receptor antagonist that increases gastric pH while reducing the volume of gastric contents (41). A number of studies (22–32, 42–50) have recently evaluated the efficacy of cimetidine premedication in increasing the pH of gastric contents. These results are encouraging and suggest that cimetidine may be superior to conventional methods for increasing the pH and decreasing the volume of gastric contents. This review considers the pharmacology and clinical utility of cimetidine in the management of patients at the risk of vomiting/regurgitation and aspiration.

H₂-Receptor Antagonists

Approximately 70 years ago, Sir Henry Dale and colleagues showed that histamine is intimately involved in gastric secretion. The classic antihistamines were found not to block this action of histamine. In 1966 Ash and Scheld (40) hypothesized that H_2-receptors were responsible for gastric secretion.

The synthesis of H_2-receptor antagonists was achieved by stepwise modifications of the histamine molecule, which resulted in nearly 700 compounds. Histamine is composed of an imidazole ring and ethylamine side chain (Fig 1, A). H_1-receptor antagonists have a modified ring or no ring at all, whereas H_2-receptor antagonists retain the ring and have modified side chains. Black et al (51) in 1972 synthesized the first H_2-receptor antagonist, burimamide, which proved to be effective in reducing histamine-stimulated acid secretion in animals and man. Because burimamide is not readily absorbed from the gut, another H_2-receptor antagonist, metiamide, structurally similar to histamine and more potent in reducing acid secretion, was synthesized (52). However, several cases of agranulocytosis were reported with the use
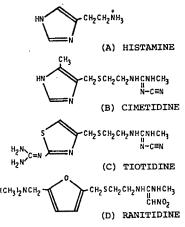
FIG 1. Structure of histamine, cimetidine, tiotidine, and ranitidine.

of metiamide (53), and it was attributed to the thiourea group in metiamide. Replacement of thiourea group in metiamide with cyanoguanidine resulted in the H_2-receptor antagonist cimetidine (54) (Fig 1, B) which had proven to be clinically effective, and soon became popular.

As clinical experience with cimetidine has increased, both the range of medical illnesses for which the drug can be used and the number of untoward effects associated with its use have increased. Hence, continuing research led to the development of several new H_2-receptor antagonists, some of which are undergoing clinical trials. Some of the new compounds undergoing clinical trials are ranitidine (55) (Fig 1, D), tiotidine (56) (Fig 1, C), oxmetidine (57), SKF 93479 (58), etinitidine (Bristol-Myers), and Sch-28080 (Schering-Plough). Clinical information is not available for some of the compounds although it is preliminary for others.

Clinical Pharmacology of Cimetidine

Pharmacokinetics

Cimetidine is a weak imidazole base, and peak blood levels are achieved 45 to 60 minutes after oral administration. The plasma half-life of cimetidine is approximately 2 hours in subjects with normal renal function (59). Walkenstein and associates (60) examined the pharmacokinetics of 300 mg of cimetidine in man after oral, intramuscular, and intravenous administration (Fig 2). Despite the fact that parenterally administered cimetidine achieves a higher peak drug level than that obtained by oral administration, clinically effective drug levels of 0.5 μg/ml are maintained for an identical period of 4 hours by either route. Similarity of plasma level curves for the intravenous and intramuscular routes of administration makes these two routes virtually interchangeable.
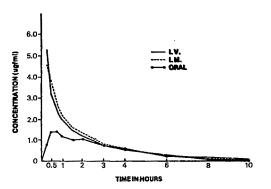
FIG 2. Mean blood levels after 300 mg of cimetidine by various routes (Adapted with permission from Walkenstein et al [60]).

Cimetidine is excreted via the kidneys within 24 hours after oral or parenteral administration, 48% to 77% of the drug being excreted unchanged (60). The rest of cimetidine is excreted in the form of metabolites, the sulfoxide being the major metabolite. Sulfoxide is a product of hepatic inactivation by conversion of the side chain thioether.

In patients with renal insufficiency, the serum half-life is increased to approximately 3 to 4 hours, and drug dosages must be reduced accordingly (61). Cimetidine is partially removed by dialysis but less so than creatinine.

Mechanism of Action

Cimetidine is a reversible, competitive H_2-receptor antagonist. In man, three endogenous acid secretogogues are histamine, gastrin, and acetylcholine. The ability of cimetidine to inhibit gastric acid secretion produced by all conventional stimuli can be interpreted as evidence that histamine is part of a final common pathway to parietal cell activation (62). A second hypothesis suggests that separate receptors exist at parietal cells for histamine, gastrin, and acetylcholine, that these interact, and that blockade of any one of them depresses responses to the remainder (62).

Antisecretory Effects

Cimetidine inhibits basal and nocturnal gastric acid secretion and acid secretion stimulated by histamine, pentagastrin, caffeine, insulin, and food (41). Hollander and associates (63) showed that a single 300-mg dose of cimetidine at bedtime resulted in at least 8 hours of significant reduction in gastric acidity in normal men. Longstreth and co-workers (64) extended these observations to patients with active duodenal ulcer and found a significant reduction of gastric acid secretion, the degree and duration of which were dose related (Fig 3). The inhibitory effect of oral cimetidine on gastric secretion begins 60 to 90 minutes after administration and reaches its peak at 120 to 150 minutes. At plasma concentrations of 0.5 μg/ml, basal secretion was suppressed by more than 80% and secretion stimulated by food or gastrin was suppressed by more than 50% (65, 66). When administered in four doses totaling 0.8 to 1.6 g, cimetidine suppressed 24-hour intragastric acidity both in normal subjects and patients with duodenal ulcers by 70% (66). The inhibitory effect of cimetidine on stimulated gastric output includes a marked decrease in both hydrogen ion concentration and gastric juice
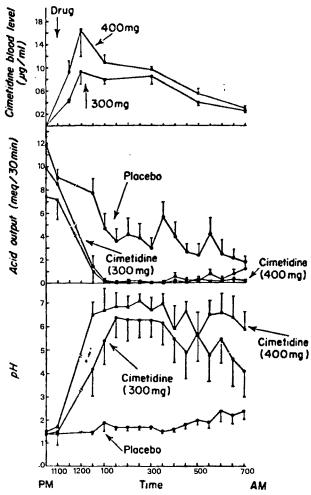
FIG 3. Effect of oral cimetidine on nocturnal gastric acidity (Reproduced with permission from Longstreth et al [64]).

volume. As cimetidine and anticholinergic agents appear to inhibit acid secretion through different mechanisms, their suppressive effect might be expected to be synergistic. Indeed it has been shown in clinical studies that combination of H_2-receptor blocker and anticholinergic agent was more effective in suppressing food-stimulated acid secretion than either drug administered alone (41, 67).

Pepsin output generally decreases in parallel with the diminished volume of gastric secretion. Output of intrinsic factor of castle in response to betazole is inhibited by cimetidine (68). Fasting serum gastrin levels of patients with duodenal ulcers appear to be unaffected by cimetidine (64). Studies of gastric output in patients with duodenal ulcers after 6 weeks of treatment with cimetidine have failed to reveal any "rebound" increase in peak acid output as compared with pretreatment levels (61). Cimetidine has no consistent effect on the rate of gastric emptying, lower esophageal sphincter pressure, or pancreatic secretion (68).

Clinical Effectiveness of Cimetidine for Premedication

The efficacy of preanesthetic cimetidine in reducing gastric pH and volume has been studied by various authors in different groups of patient populations undergoing anesthesia and surgery (22–32, 42–50). In these studies efficacy of cimetidine has been evaluated using various doses with different routes of administration, and the studies have often included comparative studies with anticholinergics as well as antacids.

Elective Surgical Patients

Single Oral Dose Regimen. This mode of administration has been studied more than the other modes of administration (22, 23, 26–30). The effect of cimetidine, 300 mg, administered orally 60 to 120 minutes before induction of anesthesia, was compared with anticholinergic and antacid premedication and was demonstrated to be significantly more effective (22, 23, 26, 28). In these clinical studies (22, 23, 26–30) 60% to 80% of elective surgical patients arrived in the operating room with gastric pH levels less than 2.5. In contrast, one dose of either 300, 400, or 600 mg of cimetidine administered in the morning or the night before surgery increased gastric pH to greater than 2.5 in 70% to 100% of patients (22, 23, 26–30).

Single Intravenous Dose Regimen. Intravenous administration of cimetidine for preoperative prophylaxis has been shown to be superior to oral administration in some clinical studies (26, 42), as higher peak plasma levels are achieved during the 1st hour after parenteral administration. Coombs et al (24) demonstrated a significant time-dependent increase in the gastric pH with a decline in gastric volume in patients receiving intravenous cimetidine 15 to 60 minutes before induction; when given 45 minutes before induction of anesthesia the gastric pH increased to greater than 2.5 in 90% of patients. Maliniak and Vakil (42) compared the efficacy of 300 mg of intravenous cimetidine with 0.3 mg of intramuscular glycopyrrolate. The mean gastric pH was 1.73 ± 0.07 before administration of cimetidine and increased to 4.43 ± 0.53 after 1 hour and to 7.23 ± 0.15 after 2 hours, whereas glycopyrrolate increased the mean gastric pH from 1.59 ± 0.05 to 2.83 ± 0.49 after 1 hour. Total acid concentration was reduced 98% after cimetidine and only 50% after glycopyrrolate.

Multiple Dose Regimen. Preanesthetic prophylaxis

by administration of multiple doses of cimetidine has been evaluated in a number of clinical trials and appears to be the most common mode of administration used by the majority of anesthesiologists in elective patients.

Keating and associates (25) and Kirkegaard et al (32) demonstrated that cimetidine administered orally the night before surgery and again in the morning in doses of 300 and 400 mg increased gastric pH to greater than 2.5 in 67% and 75% of patients, respectively. In a similar study by Weber and Hirshman (26) the gastric pH increased to greater than 2.5 in 90% of patients after 300 mg of cimetidine with a mean of 5.1 ± 0.61. Weber and Hirshman also studied the combination of oral cimetidine, 300 mg, administered the night before surgery plus 300 mg of intramuscular cimetidine administered 60 to 90 minutes before induction. This increased gastric pH to greater than 5.0 in all patients to a mean level of 7.3 ± 0.31. This method is described by the same authors (26) as superior and more effective than the other modes of administration (Fig 4). Toung and Cameron (31) evaluated the effect of combination of cimetidine, 300 mg, administered orally at 14 hours and 8 hours, and 300 mg of intravenous cimetidine administered 60 to 90 minutes before induction of anesthesia. This mode increased gastric pH to greater than 2.5 in 93% of patients and effectively reduced gastric fluid volume.

Emergency Surgery

Patients having emergency surgery pose high risk
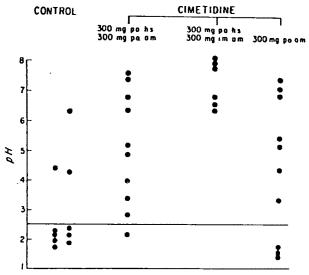
FIG 4. Distribution of gastric pH values in control and cimetidine-treated patients (Reproduced with permission from Weber and Hirshman [26]).

of pulmonary aspiration. Unfortunately, reports of experience with cimetidine prophylaxis in patients seen for emergency surgery are limited to a small number of patients. Dobb and associates (43) studied the effect of 200 mg of cimetidine administered intravenously to 20 patients scheduled for emergency surgery and expected to have "full stomachs." The gastric pH was evaluated at greater than 2.5 in 80% of patients 1 hour after cimetidine administration and was greater than 4.0 in all the patients after induction of anesthesia.

Obstetric Anesthesia

The potential for prophylactic preoperative H_2-receptor blockade appears to be great in obstetric anesthesia, as aspiration stands out as a prominent cause of maternal mortality and morbidity, even with present advances in the management of parturient. Safety and efficacy of cimetidine prophylaxis in obstetric anesthesia have been reported by several investigators (45–49, 69, 70). It has been studied in more obstetric patients undergoing anesthesia than in any other group of patients.

Husemeyer and Davenport (45) compared cimetidine, 300 mg, administered orally 2 to 6 hours before surgery with magnesium trisilicate, 20 ml, administered 60 minutes before induction. The gastric pH in patients given cimetidine was greater than 2.5 in 77.5% of patients whereas it was greater than 2.5 in all patients given the antacid. Pickering and co-workers (46) demonstrated that intramuscular cimetidine, 300 mg, increased gastric pH to greater than 2.5 in 77.7% of patients whereas Gelusil, 30 ml, was effective in 75% of patients when administered 1 hour before induction.

Dundee and associates (47–49) described their experience with cimetidine in obstetric anesthesia in approximately 5000 patients for preanesthetic prophylaxis. Preliminary trials of intravenous and oral cimetidine were followed by a large field trial in which a 400-mg oral loading dose was given at establishment of labor followed by 200 mg every 2 hours. In the patients who received 200 mg of cimetidine intravenously 60 to 80 minutes before induction of anesthesia, gastric pH was greater than 2.5 in all. One third of patients had gastric pH less than 2.5 when the interval between administration of the drug and induction of anesthesia was 30 to 40 minutes or more than 90 minutes (47). In the field trial only 4% of patients had gastric pH less than 2.5 when cimetidine was administered.

Pediatric Anesthesia

Reports of clinical experience with the use of cimetidine in neonates and children for either hypersecretory conditions or for preanesthetic prophylaxis are limited. Goudsouzian and colleagues (34) found that cimetidine administered orally on the morning of surgery reduces the volume and acidity of gastric fluid in infants and children. All children studied who had not been given cimetidine had gastric pH levels less than 2.5 whereas cimetidine (2.5 to 10 mg/kg) increased the pH of gastric contents and reduced the volume of gastric aspirate. The ED_{95} of cimetidine that produced pH values greater than 2.5 was 7.5 mg/kg, and the mean gastric pH was 6.16 ± 0.38. At a dose of 10 mg/kg, all the children had gastric pH greater than 3.5 with a mean of 6.36 ± 0.33. Cimetidine was most effective when given orally between 1 and 4 hours before gastric specimens were obtained.

Morbidly Obese Patients

Increased risk of aspiration of gastric contents in morbidly obese patients was demonstrated by Vaughn et al (19). Wilson and co-workers (50) studied the efficacy of cimetidine in morbidly obese patients undergoing elective surgery. Cimetidine, 300 mg, was administered orally at midnight and 90 to 120 minutes before induction of anesthesia. They found that cimetidine increased gastric pH to greater than 2.5 in 85% of patients to a mean level of 5.0 ± 0.6, whereas glycopyrrolate and atropine were effective only in 38% and 33% of patients with mean gastric pH levels of 2.4 ± 0.4 and 2.7 ± 0.6, respectively. In addition, cimetidine reduced the volume of gastric contents significantly.

Side Effects and Toxicity of Cimetidine

Cimetidine was released for clinical use in the United Kingdom in November 1976, and in the United States in August 1977. Since then no other H_2 antagonist has been freely available. The Food and Drug Administration approved cimetidine for the treatment of duodenal ulcer disease and the Zollinger-Ellison syndrome in the United States. The number of approved indications is greater in the United Kingdom than in the United States.

Histamine receptors are widely distributed in the various tissues and organs of the body, including the heart, blood vessels, bone marrow, pituitary gland, and hypothalamus, as well as the other areas of the brain. Side effects and toxicity may be produced either by blockade of these receptors or by idiosyncratic reactions.

Cimetidine is generally well tolerated. Adverse effects during short-term therapy, including headache, dizziness, fatigue, muscle pain, fever, constipation or diarrhea, and skin rashes occur in less than 2% of the patients. Drug-related elevations of serum transaminase levels have been noted, but serum transaminase has promptly returned to pretreatment levels either during the period of drug administration or after treatment has been discontinued. Rarely, unexplained elevations in alkaline phosphatase levels have also been noted. Even though no associated liver function abnormalities have been observed in the vast majority of patients, biopsy-proven periportal hepatic necrosis and centrilobular necrosis have been reported in two patients.

A weak antiandrogenic effect has been noted in rats and dogs given high doses of cimetidine. Gynecomastia in men and galactorrhea in women have been reported in a small number of patients. Several of these patients had the Zollinger-Ellison syndrome and had been receiving the drug for more than 3 months.

Slight elevation of serum creatinine levels occurs without renal dysfunction in many patients on cimetidine therapy. Generally, the increase is not so great that serum creatinine levels exceed the normal range, but levels greater than 2 mg/dl have been found in 3% of patients. In most instances elevations of serum creatinine levels have been transient or have remained within the normal range even during continued treatment. The levels usually return to normal with cessation of treatment. In chronic renal failure, treatment with cimetidine does not appear to cause any impairment of glomerular filtration. Observed increases in serum creatinine livers might be caused by reversible inhibition of tubular secretion of creatinine by cimetidine. Changes in serum creatinine levels may, however, be of clinical importance as cimetidine treatment may invalidate serum creatinine and creatinine clearance as standard tests of glomerular filtration, especially in patients having renal transplants (71). In patients with chronic renal failure and in the elderly or debilited patients, the doses of cimetidine and the frequency of administration should be decreased.

Despite poor penetration by cimetidine of the central nervous system in animals, neural dysfunction has been encountered, particularly with high doses in elderly patients and in association with renal dysfunction. There have been infrequent reports of agitation, mental confusion, and coma, with improve-

ment occurring on cessation of the therapy (72–74). Schentag et al (74) reported changes in mental status in six of 36 critically ill patients when serum cimetidine levels were greater than 1.25 μg/ml. They also found the ratio between cerebrospinal fluid and serum levels of cimetidine to be 0.24:1 in these six patients, all of whom had combined hepatic and renal dysfunction. In all the cases, reduction of cimetidine dosage improved the mental status. However, mental confusion has been reported at lower than therapeutic serum levels of cimetidine (<0.5 μg/ml). In critically ill patients with azotemia, abnormal drug access to the central nervous system could be due to the increased permeability of the blood-brain barrier associated with uremia (75). Mogelnicki and colleagues also reported arousal following physostigmine in two such cases (75).

Bradycardia, hypotension, cardiac arrythmias, and cardiac arrest have been reported following intravenous cimetidine (76–79). Data from in vivo animal studies (51) and from in vitro studies of human right atrial fibers (80) indicate that histamine-enhanced automaticity is antagonized by H_2-receptor antagonists. Engel and Luck (80) were unable to detect any sinus node dysfunction caused by cimetidine in a small series of patients, whereas Samuel and Dundee (81) demonstrated little or no change in cardiovascular function in 10 critically ill patients after injection of a 400-mg bolus of cimetidine. It is nevertheless recommended that routes of administration other than the intravenous be used or that diluted solutions be slowly infused over a period of at least 30 minutes (77, 79).

Hematologic abnormalities and bone marrow suppression associated with cimetidine therapy have been reported by various clinicians (82–88). This association is noteworthy because the potential consequences of bone marrow suppression are serious and metiamide, the first H_2-receptor antagonist used in man was withdrawn from human use because of its adverse effect of granulocytopenia, including one case of fatal agranulocytosis (53, 85). But cimetidine differs from metiamide structurally and, unlike metiamide, tritiated cimetidine is not taken up by precursor cells in bone marrow (89). Cimetidine, 506 mg/kg, did not cause granulocytopenia in dogs whereas only 80 mg/kg of metiamide produced this effect. Moreover, in three patients who developed granulocytopenia with metiamide, when cimetidine was substituted for metiamide the granulocytopenia disappeared (90, 91). No granulocytopenia could be attributed to cimetidine in more than 4000 patients studied prospectively

in clinical trials. Twenty-six cases of hematologic abnormalities, usually granulocytopenia, had undergone Food and Drug Administration evaluation in 1978, at which time the drug had been used in 1.3 million people (92). Most of the cases were associated with complex medical problems, concomitant medications, and serious illnesses. Granulocytopenia was conclusively attributed to cimetidine in some cases (85, 87, 88) and was dose related in one case (87). In some cases, cause and effect relationship could not be determined. Finally, the incidence of leukopenia is reported as 1/100,000 patients, whereas agranulocytosis and thrombocytopenia are reported as 3/1,000,000 patients. It is encouraging to note the absence of reports of granulocytopenia in patients given prophylactic cimetidine before anesthesia.

Busse and Sosmon (93) suggested that asthmatic patients may have an imbalance of H_1- and H_2-receptors with a relative decrease in H_2-receptors. They also found a decreased number of H_2-receptors on granulocytes of asthmatic patients. Later, Nathan et al (94, 95) presented evidence that histamine in the airways of asthmatic patients mediates bronchoconstriction via the H_1-receptors while it produces bronchodilation via the H_2-receptors. In their studies, administration of cimetidine potentiated histamine-induced bronchospasm. A single oral dose of cimetidine decreased the threshold dose of inhaled histamine producing bronchoconstriction (94). These reports suggest that cimetidine should be administered with caution in asthmatic patients.

Cimetidine crosses the placental barrier and is excreted in maternal milk. Studies in animals have shown no teratogenic effect attributable to cimetidine at dose ranges of 100 to 950 mg/kg/day. In human studies, cimetidine has no effect on the mother, baby, or progress of labor (69, 70).

Clinical experience with cimetidine in children and neonates is, as mentioned above, limited. Although cimetidine therapy was reported to be free of side effects in newborns by Chhattriwalla and colleagues (96), other investigators (97–99) have reported both hepatic (transient cholestasis) and cerebral toxicity. Elevation of serum levels of bile acids and other aberrations in liver function return, however, to pre-cimetidine levels shortly after or even during treatment (97), although cerebral side effects resolve only after discontinuation of the drug (98, 99).

Inhibition of drug metabolism by cimetidine is an important drug interaction. There is increasing evidence (100–104) that demonstrates that cimetidine inhibits microsomal drug metabolism in the liver.

This action of cimetidine is also seen with other imidazole ring compounds, due, perhaps, to binding to microsomal P-450 (100). As a result of the effect of cimetidine on microsomal P-450 activity, the half-life of antipyrine is increased by cimetidine due to decreases in clearance (101). Similarly, the metabolism of anticoagulants, barbiturates, benzodiazepines, propranolol, and theophylline is decreased and the duration of action increased by cimetidine. Serlin et al (101) have shown that cimetidine prolongs prothrombin time in patients given oral anticoagulants of both coumarin and indenadione derivatives. Desmond et al (102) have demonstrated severe impairment of elimination of chlordiazepoxide in man after pretreatment with cimetidine for 7 days at normal therapeutic doses, whereas Klotz and Reimann (103) reported 43% reduction of clearance of diazepam in volunteers given cimetidine. Lam and Parkin (105) reported a case of prolonged postoperative somnolence with the combination of cimetidine and diazepam. Feely and co-workers (104) convincingly demonstrated an interaction between cimetidine and propranolol and indicated that cimetidine not only decreases liver blood flow, as does propranolol, but independently decreases the rate of metabolism of propranolol. The dependence of lidocaine clearance on hepatic blood flow is known. Hence, cimetidine may also interfere with clearance of lidocaine. The above interactions of cimetidine with other drugs will influence the clinical practice of the anesthesiologist. No significant interactions were seen in acute intravenous studies in the rat (106) with atropine, diazepam, thiopental, meperidine, succinylcholine, d-tubocurarine, norepinephrine, epinephrine, ampicillin, and cephalothin.

New H₂-Receptor Antagonists

Initial evidence suggested that to function as a H₂-receptor antagonist a drug must be an analogue of histamine and contain an imidazole ring. However, the development of new, nonimidazole H₂-receptor antagonists has demonstrated that in human gastric mucosa, recognition of H₂-receptors is not exclusively determined by the imidazole nucleus. Cimetidine, like histamine, contains an imidazole ring. Most of the new compounds, however, have structures that are different from that of cimetidine with the exception of oxmetidine in which the cyanoguanidine moiety of cimetidine has been replaced by isocytosine. Ranitidine and SKF 93479 contain furan rings whereas tiotidine contains a thiazole ring (Fig 1).

Ranitidine (Fig 1, D) is a substituted amino-alkyl

furan derivative which markedly inhibits basal and nocturnal gastric acid secretion as well as secretion stimulated by histamine, pentagastrin, sham-feeding, and meals (107–116). Ranitidine is rapidly absorbed after oral administration, achieving peak plasma levels after 60 to 90 minutes; therapeutically effective plasma concentrations last at least 8 hours (110). The bioavailability of oral ranitidine is 50% of the bioavailability of intravenous ranitidine (110). Most of the drug is excreted in urine unchanged with an elimination half-life of approximately 2 hours (111). On a molar basis, ranitidine is 4 to 7 times more active than cimetidine as an antisecretory agent. Dammann and associates (114) have shown in two different studies that a single dose of 100 mg of oral ranitidine increased gastric pH to greater than 7.0 for 7 to 8 hours, whereas a single dose of 150 mg administered orally suppressed basal acid output by 70% and pentagastrin-stimulated secretion by 40% in healthy volunteers. In addition, 150 mg of ranitidine administered orally three times daily produced gastric pH values of 7.0 for 24 hours in patients undergoing parenteral nutrition with previous intragastric pH levels of 2.0 or less (Fig 5); an average gastric pH of 4 was maintained even 12 hours after the last dose of ranitidine. In a report by Pedan and co-workers (108), nearly total inhibition of acid secretion was achieved during a 12-hour overnight period after a single oral dose of
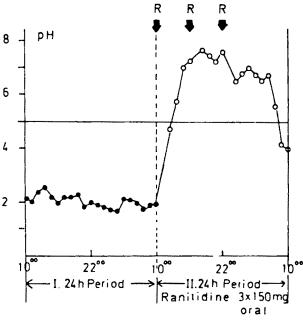
Fig 5. Effect of oral ranitidine (150 mg three times a day) on intragastric pH profile in patients undergoing parenteral nutrition (Reproduced with permission from Dammann et al [114]).

80 mg of ranitidine with a standard evening meal, whereas cimetidine, 300 mg, inhibited only 66% of acid secretion. In preliminary clinical studies (113) ranitidine dose of only 100 mg twice daily exerted beneficial effects on duodenal ulceration with a healing rate that was at least as favorable as with standard cimetidine regimen. Johnston and co-workers (116) compared the efficacy of ranitidine for preoperative prophylaxis with that of cimetidine administered orally or intravenously. Compared with placebo, 400 mg of cimetidine administered either orally or intravenously consistently increased gastric pH to greater than 2.5 and reduced the volume in all the patients only when administered 2 to 3 hours before induction of anesthesia, whereas ranitidine, 80 mg intravenously or 150 mg orally, produced a similar effect when administered 2 to 7 hours before induction. During short-term clinical evaluations and toxicologic studies by the manufacturer, there were no obvious side effects that would preclude the use of this new compound in man. Ranitidine does not inhibit drug metabolism by microsomal enzyme systems as does cimetidine when given in equipotent doses (117-119).

Tiotidine, a highly specific competitive H_2-antagonist, differs structurally from cimetidine in the heterocyclic moiety while resembling cimetidine in having an identical side chain (Fig 1, C). In conscious dogs, tiotidine is at least 10 times more potent than cimetidine as an inhibitor of histamine-stimulated gastric secretion (120). Tiotidine has demonstrated potent and long-acting H_2-receptor blocking activity in healthy human volunteers, as well as in patients with duodenal ulcers (121-123). Tiotidine is well absorbed after oral administration with an elimination half-life of approximately 2½ hours (123). Although tiotidine is 10 times more potent than cimetidine on molar basis, oral tiotidine is only approximately 3 times more potent than an equal dose of cimetidine due to major differences in bioavailability (123). Valenzuela et al (121) demonstrated prolonged, dose-related reduction of nocturnal acid secretion after 25-, 50-, 100-, and 150-mg doses of oral tiotidine. The inhibition of hydrogen ion secretion was, respectively, 80%, 89%, 96%, and 98% of that observed after placebo, whereas 300 mg of cimetidine caused 87% inhibition. Richardson et al (122) have shown that 300 mg of oral tiotidine was more effective than 300 mg of oral cimetidine in suppressing food-stimulated acid secretion in patients with duodenal ulcers (Fig 6). Longer duration of action was demonstrated by the fact that from 5 to 7 hours after administration, acid secretion was inhibited 80% and 97% by 150 and 300
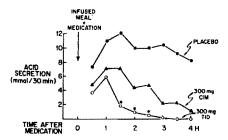
FIG 6. Comparison of effect of placebo, 300 mg of cimetidine, or 300 mg of tiotidine on mean acid secretion in response to an infused steak meal in patients with duodenal ulcers (Reproduced with permission from Richardson et al [121]).

mg of oral tiotidine, respectively, with significant suppression lasting more than 12 hours. There have been no major side effects observed in preliminary clincal reports and tiotidine has been shown experimentally to be devoid of antiandrogenic and cardiac effects in concentrations producing adequate H_2-receptor blockade (124).

Oxmetidine (SKF 92994), an imidazole derivative, differs from cimetidine in that it has an isocytosine ring instead of cyanoguanidine in the side chain (57, 125). Even though animal data suggest that oxmetidine is longer acting and more potent than cimetidine, its effect in man on nocturnal and food-stimulated acid secretion appears to be similar to that of cimetidine in duration after oral administration (57). It is 8 to 10 times more potent than cimetidine on molar basis, but the oral compound is only twice as potent as cimetidine. Oxmetidine, unlike cimetidine, does not inhibit mixed function oxidase-mediated drug elimination (119).

SKF 93479, a furan derivative, is a potent, long-acting highly selective H_2-receptor antagonist (58, 126). Preliminary results suggest that the significant antisecretory effect is maintained for 8 hours and that on a molar basis it is approximately 10 to 20 times more potent than cimetidine. It is well absorbed after oral administration with a mean elimination half-life of approximately 5 hours (126). No untoward effects have been noted in the preliminary clinical studies which involve a small number of patients:

Discussion

Although cimetidine is approved only for the treatment of peptic ulcer disease and the Zollinger-Ellison syndrome in the United States, it is frequently used with benefit in various other conditions such as gastric ulcer, esophagitis, acute gastrointestinal hemorrhage in liver disease, pancreatic insufficiency, prophylaxis against stress ulceration, and as a premedicant before

induction of anesthesia to increase the pH and reduce the volume of gastric secretions. A large number of ' patients undergoing surgery are at risk of pulmonary damage if tracheal aspiration of gastric contents should occur. Sudden regurgitation, imcompetence of lower esophageal sphincter, gastric hypersecretion, gastric dilation, position-dependent reflux, and unexpected difficult tracheal intubations are all predisposing factors for aspiration. As Coombs and Hooper (127) also point out, the risk of acid gastric pH may extend throughout the operation, and extubation may be as hazardous as intubation. Hence, the desirability of increasing the gastric fluid pH toward neutral and reducing the gastric volume before induction of anesthesia.

Presently antacids, anticholinergics, cimetidine, and metoclopramide are available for prophylaxis. The value of antacids and anticholinergics is questionable. Metoclopramide, recently approved for the treatment of esophageal reflux, stimulates the motility of upper gastrointestinal tract without stimulating gastric, bilary, or pancreatic secretions (128). The exact mechanism of its action is unclear, but the effect on motility can be abolished by anticholinergic drugs. Most likely, the gastric pH is minimally affected by metoclopramide. Metoclopramide may, however, produce sedation and extrapyramidal reactions (128). Experience with metoclopramide is limited at present, so conclusions cannot be drawn regarding its possible use for prophylaxis to reduce gastric volume and acidity. Among the available agents for clinical use, cimetidine offers a relatively easy, effective, and reliable pharmacologic approach to increasing gastric pH.

The effects of cimetidine on the gastric pH and volume have been fairly well studied in elective surgical patients. It appears certain that cimetidine increases gastric pH to a relatively safe range in at least 67% of patients, and, indeed, it has been reported to be effective in 100% of patients in several studies. Unfortunately, published experience of cimetidine use in emergency and pediatric anesthesia is limited to small numbers of patients. Results are encouraging in these clinical trials, as cimetidine increased the pH to greater than 2.5 in 80% of the patients having emergency surgery and 100% of pediatric patients. The available clinical data from several studies in obstetric anesthesia show its efficacy in increasing gastric pH without concomitant increase in gastric volume in patients undergoing cesarean section with no adverse effects on the parturient or the fetus, or on progress of labor (45–49, 69, 70). Even though H_2-receptors are found in the myometrium of the uterus,

no significant effects of cimetidine on uterine function have been found in humans or animals (69, 70). To date, we are not aware of any clinical reports evaluating efficacy of cimetidine prophylaxis in ambulatory surgical patients. Hence clinical trials are warranted in ambulatory surgical patients; there is scope for further clinical trials in patients undergoing emergency surgery, in morbidly obese individuals, and in neonates, infants, and children.

Even though it appears certain that cimetidine increases gastric pH, it also appears to be equally certain that its action on gastric volume is variable. Some investigators find no significant reduction in gastric volume at the time of induction of anesthesia with cimetidine prophylaxis. Others have found cimetidine effective in reducing gastric volume. The potentiation of the inhibitory action of cimetidine on H_2-receptors by simultaneous administration of anticholinergics reported by Richardson (41) and Feldman et al (67) may prove to be clinically useful in clinical practice.

Concerning the route of administration, parenteral administration is claimed to be superior to oral administration (24, 26, 31, 42, 43). Although onset of action is faster and an earlier peak inhibitory effect is seen with parenteral routes of administration, clinically effective serum levels are maintained for 4 hours by either route. However, rapid intravenous administration of cimetidine is usually ill advised, given the possibility of untoward cardiovascular system effects. Intramuscular cimetidine is safe and acceptable without any untoward systemic or local reactions (129).

Multiple-dose regimens for administration of cimetidine appear to be more effective than single doses, especially when oral cimetidine is used. Weber and Hirshman (26) found, in their study of different regimens, oral cimetidine, 300 mg, at bedtime with an intramuscular dose of 300 mg of oral cimetidine in the morning to be superior to all other regimens (Fig 4); 300 mg of oral cimetidine at bedtime and in the morning was the second choice. The interval between the administration of cimetidine and induction of anesthesia plays an important role because the onset of action of cimetidine occurs after 60 to 90 minutes with the peak inhibitory action occurring 120 to 150 minutes after oral administration. The value of the bedtime dose is stressed, because although cimetidine reduces or stops production of gastric acid, it does not influence the pH of gastric contents already present (25, 30, 47). Duration of the effect of cimetidine is such that for most procedures lasting up to 3 hours, the gastric residue pH is likely to remain greater than 2.5, thus providing protection during perioperative

period and at the time of extubation (25, 30, 43, 127). It will be interesting to see the effect of preoperative cimetidine prophylaxis on the frequency of silent regurgitation under anesthesia in well controlled clinical studies. Even though experience to date is limited, Joyce and co-workers (130) reported minimal pulmonary lesions in rabbits with the aspiration of strained liquid gastric contents after cimetidine treatment.

Kruss and Litmand (131) concluded that the cimetidine is safe enough to be given under supervision for periods not exceeding 8 weeks. So far, no complications have been reported in various clinical studies conducted to evaluate the ability of cimetidine to increase the gastric pH before surgery in elective or emergency surgery and in pediatric or obstetric patients. Drug interaction with benzodiazepines may, however, prolong recovery from general anesthesia. In these cases physostigmine maay be of value in reversing the sedation as it is claimed to reverse the sedation produced by cimetidine (75) as well as diazepam (132).

It should be remembered that increasing the gastric fluid pH toward neutral is not a guarantee against regurgitation or aspiration and will not replace expert, vigilant anesthetic administration. However, if properly applied, H_2-receptor blockade may significantly reduce the perioperative risk of acid aspiration and resultant pulmonary injury. As cimetidine is the only H_2-receptor blocker approved for clinical use, it is the choice drug in day-to-day clinical practice of anesthesia. Hence, routine inclusion of cimetidine in the preoperative therapy has been suggested, preferably in addition to glycopyrrolate. Even though results with parenteral administration are impressive, a multidose oral regimen appears to be relatively easy and effective. This includes 300 mg in adults and 7.5 mg/kg in liquid form in children administered orally at bedtime and in the morning, with a repeat dose after 4 to 5 hours. Parenteral administration either by intramuscular route or slow intravenous infusion is recommended for patients with a high index of suspicion of vomiting and regurgitation; these include patients with full stomach, suspected difficult intubation, and hiatal hernia with esophageal reflux, as well as morbidly obese and obstetric patients.

New H_2-receptor antagonists appear to be more potent and longer acting than cimetidine in clinical trials. Due to their higher antagonistic activity, these new H_2-receptor antagonists may have fewer side effects than cimetidine, and in the short-term clinical trials in humans, no evidence of serious side effects

has emerged. Ranitidine and oxmetidine (117–119) do not inhibit microsomal enzyme metabolism of drugs in the liver in clinical doses. The effect of tiotidine on drug interactions is not known yet, but it apparently does not affect cardiac function (124). Ranitidine has been shown to be effective for preanesthetic prophylaxis even 7 hours after the drug was administered, demonstrating its beneficial prolonged action. Proven high potency and prolonged action with probable minimal side effects and noninterference with drug metabolism of these agents will add to the safety and efficacy of preoperative prophylaxis against acid aspiration. One of these new H_2-receptor blockers may emerge as an ideal agent in the near future. We look forward to further clinical trials aimed at increasing the gastric pH and reducing the gastric volume for prophylaxis in the surgical patient population undergoing anesthesia.

As cimetidine is not approved by the Food and Drug Administration for preoperative prophylaxis, caution should be exercised in prescribing it to patients with medical illnesses, especially renal and hepatic failure, and especially geriatric and pediatric patients. It may be necessary to obtain institutional approval for routine preoperative administration.

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technical
COMMUNICATION

Dependence of Microsomal Methoxyflurane *O*-Demethylation on Cytochrome P-450 Reductase and the Stoichiometry of Fluoride Ion and Formaldehyde Release

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In order to characterize further the in vitro liver microsomal O-demethylation and defluorination of the volatile anesthetic methoxyflurane, and obtain additional information regarding the participation of cytochrome P-450 in the oxidation, the stoichiometry of the reaction was determined and the effect of antibody to cytochrome P-450 reductase on this unique biotransformation was examined. Liver microsomes were isolated from rabbits and rats in which enzyme induction had previously been produced by phenobarbital. The O-demethylation of methoxyflurane by phenobarbital-induced microsomes results in the production of 1 mol of formaldehyde for every 2 mol of fluoride ion produced. Dichloroacetic acid is also a product of methoxyflurane O-demethylation. Antibody to cytochrome P-450 reductase inhibits by 85% the amount of fluoride ion produced by the microsomal metabolism of methoxyflurane. Thus critical indirect supportive data are contributed to the hypothesis that at least one, but perhaps more, cytochrome P-450 is indeed responsible for methoxyflurane O-demethylation and defluorination.

Key Words: ANESTHETICS, Volatile: methoxyflurane; BIOTRANSFORMATION (Drug): methoxyflurane.

Isoflurane $(CF_3CHClOCHF_2)$, enflurane $(CHF_2 \cdot OCF_2CHClF)$, and methoxyflurane $(CH_3OCF_2 \cdot CHCl_2)$ are three volatile anesthetics with similar chemical structures. Each anesthetic is a halogenated ethyl methyl ether. Methoxyflurane is seldom used today because of its nephrotoxicity, whereas enflurane and isoflurane are clinically important volatile anesthetics. Under certain circumstances enflurane is thought to be minimally nephrotoxic due to its metabolism to fluoride ion (1). The recently introduced anesthetic, isoflurane, has not yet been implicated in any toxic reaction. Methoxyflurane, in contrast to enflurane and isoflurane, is extensively metabolized to readily quantitated metabolites. Therefore, we have elected to use methoxyflurane as a model anesthetic to learn more about the metabolism of the clinically important volatile anesthetics.

This paper is concerned with the *O*-demethylation and defluorination pathway of methoxyflurane metabolism rather than the dechlorination pathway (Figure). The reasons for this choice are 2-fold. First, several of the metabolites of the *O*-demethylation (but not the dechlorination) pathway can be directly and readily quantitated. Second, the fluoride ion produced by *O*-demethylation is nephrotoxic. *O*-Demethylation is, therefore, a clinically important route of methoxyflurane metabolism. At present, it is not known whether methoxydifluoroacetic acid, the major metabolite of methoxyflurane in man, is metabolized to produce fluoride ion (2).

FIGURE. Hypothetical pathway of methoxyflurane metabolism by cytochrome(s) P-450. O-Demethylation pathway is shown on right; dechlorination pathway is shown on left.

The cytochromes P-450 are a family of mixed-function oxidases found in high concentration in the endoplasmic reticulum of the liver. They are responsible for the metabolism of a variety of xenobiotics, carcinogens, and endogenous compounds such as steroids, prostaglandins, vitamin D, and fatty acids. Each cytochrome P-450 possesses a unique substrate specificity which frequently overlaps with that of another cytochrome P-450. It is possible for more than one form of a cytochrome P-450 to metabolize the same substrate. However, the different cytochromes P-450 would metabolize the substrate at different rates and frequently yield different products.

The evidence presented in this paper, namely, the dependence of methoxyflurane biotransformation on cytochrome P-450 reductase and the demonstration that this reaction is an oxidative process with the expected stoichiometry of a cytochrome P-450 catalyzed reaction, in addition to that provided by a number of other investigators, suggests that one or more cytochrome P-450 is involved in the O-demethylation of methoxyflurane (3–8). The indirect evidence provided by other researchers on this question includes the facts that the O-demethylation of methoxyflurane: (a) is catalyzed by a liver microsomal enzyme (3, 4); (b) is inhibited by carbon monoxide, SKF-525A, and metyrapone, all moderately specific

cytochrome P-450 inhibitors (3, 7); (c) is induced by prior treatment of the animal with phenobarbital, a known inducer of cytochrome P-450 and other enzymes (3, 4, 7, 8); (d) is decreased when the three hydrogen atoms on the methoxy group are substituted with deuterium atoms [this evidence is consistent with the proposed mechanism of oxidation of the carbon-hydrogen bond by cytochrome P-450 which is thought to proceed by an initial hydrogen abstraction to give a carbon radical intermediate (9)]; and (e) requires oxygen and nicotinamide-adenine dinucleotide phosphate (NADPH) (3–5, 7). Furthermore, O-dealkylation of xenobiotics is a reaction characteristically catalyzed by cytochrome P-450 (10). These numerous indirect lines of evidence all suggest that cytochrome(s) P-450 catalyzes methoxyflurane O-demethylation. But, no single piece of this body of evidence is a direct, conclusive demonstration that cytochrome(s) P-450 really does O-demethylate methoxyflurane (11). The studies of methoxyflurane metabolism described in this paper provide further information about liver microsomal O-demethylation of a volatile anesthetic and the role of cytochrome P-450 in this process.

Methods

Male New Zealand rabbits weighing 2 kg each, and male Fischer 344 rats weighing 200 g each, were given phenobarbital to produce hepatic microsomal enzyme induction. Phenobarbital was added to the animals' drinking water at a final concentration of 1 mg/ml for 7 days before they were killed. The animals fasted for 12 hours before they were killed. Microsomes were isolated as described by Haugen et al (10). The reaction mixture contained 1 mg/ml of microsomal protein, 1 unit per milliliter of glucose-6-phosphate dehydrogenase, 5 mM glucose-6-phosphate, 1 mM NADP, 0.05 M tris(hydroxymethyl)aminomethane (Tris) buffer at pH 7.4 and 1 μl of methoxyflurane. The reaction was performed in closed vials at 37°C for 30 minutes in a shaking water bath during which time the metabolism of methoxyflurane was linear. It was terminated by heating in a 75°C water bath for 2 minutes if fluoride ion was measured or by the addition of trichloroacetic acid to a final concentration of 7% if formaldehyde was measured. Appropriate standards of formaldehyde and fluoride ion were used. In the incubation mixtures with rat microsomes it was necessary to add ethylenediaminetetraacetic acid (EDTA) to a final concentration of 1 mM. Formaldehyde was measured as described by Nash (12).

Fluoride ion concentration was measured with an Orion fluoride-ion specific electrode.

Dichloroacetic acid was detected using the following procedure which was developed in our laboratory. The sample to be examined (either a solution containing a known amount of dichloroacetic acid or the liver microsomal reaction mixture) was acidified to pH 1 with HCl and extracted six times with an equal volume of diethyl ether. An excess of diazomethane in diethyl ether was added to the microsomal extract. The mixture was allowed to stand at room temperature in a closed vial for 2 hours. It was then evaporated to approximately 0.5 ml under a stream of nitrogen. Toluene, 0.5 ml, was added to the resulting solution to decrease its volatility. The toluene and diethyl ether mixture (2 μl), containing the methyl ester of dichloroacetic acid, was injected into a Varian 5730A gas chromatograph equipped with a Ni[63] electron capture detector. A ⅛-in diameter, 4-ft long glass column packed with Chromosorb-101 was used. Temperatures of the injector, column, and detector were 210°C, 160°C, and 260°C, respectively. The carrier gas was argon/methane (95%/5%) with a 60-ml/min flow rate. The retention time of an authentic sample of the methyl ester of dichloroacetic acid was identical with that of the dichloroacetic acid and the microsomal reaction mixture that had been subjected to the previously described procedure.

The antibody to rabbit cytochrome P-450 reductase and control gamma-globulin were supplied by Drs. Eric Johnson and U. Müller-Eberhard. The antibody to the purified cytochrome P-450 reductase was raised in goats.

Results and Discussion

The experiments were performed with liver microsomes isolated from phenobarbital-induced animals so that metabolism of methoxyflurane by microsomes

would produce readily quantifiable levels of metabolites. The data obtained when liver microsomes were treated with antibody to cytochrome P-450 reductase are shown in Table 1. These results demonstrate that antibody against cytochrome P-450 reductase, but not control gamma-globulin, inhibits the microsomal O-demethylation of methoxyflurane by 85%. In control experiments it could be demonstrated that the microsomal metabolism of benzphetamine, a compound known to be metabolized by purified reconstituted cytochrome P-450, is inhibited by 80% using a similar ratio of antibody to cytochrome P-450 reductase (data not shown). Also, purified cytochrome P-450 reductase was shown not to O-demethylate methoxyflurane (E. Canova-Davis and L. Waskell, unpublished observations).

Our demonstration of the dependence of methoxyflurane microsomal O-demethylation on cytochrome P-450 reductase argues strongly that cytochrome(s) P-450 catalyzes the O-demethylation. However, it is not direct proof of this fact as another enzyme called heme oxygenase, which is not a cytochrome P-450, nevertheless requires cytochrome P-450 reductase for activity in converting hemin to biliverdin (13) both in microsomes and a reconstituted system.

The data presented in Table 2 reveal that 2 mol of fluoride ion are produced by liver microsomal metabolism of methoxyflurane for every 1 mol of formaldehyde produced. This is the expected stoichiometry

TABLE 1

Inhibition of Methoxyflurane O-Demethylation in Rabbit Liver Microsomes by Antibody to Cytochrome P-450 Reductase*

	F⁻†
Complete system + control I_g	75
Complete system + ab to cytochrome P-450 reductase	11

* This reaction was carried out as described under "Methods." Control immunoglobulin and antibody to cytochrome P-450 reductase were added to the reaction mixture to a final concentration of 5 mg of protein per milliliter.

† Nanomoles of fluoride ion (F⁻) produced per milligram microsomal protein per hour.

TABLE 2

Production of Formaldehyde (CH_2O) and Fluoride Ion (F^-) from Methoxyflurane by Hepatic Microsomes*

	Phenobarbital-induced species	
	Rat	Rabbit
Nmol of cytochrome P-450/ mg of microsomal protein	2.36 ± 0.25	3.38 ± 0.3
Nmol of CH_2O produced/mg of microsomal protein/30 min	12.5 ± 0.18	21.0 ± 3.95
Nmol of CH_2O produced/ nmol of cytochrome P-450	5.3 ± 0.01	6.26 ± 1.15
Nmol of F^- produced/mg of microsomal protein/30 min	26.0 ± 3.2	43.8 ± 7
Nmol of F^- produced/nmol of cytochrome P-450/30 min	11.0 ± 1.4	12.9 ± 2.14
Ratio of F^-/CH_2O	2.1	2.07

* These experiments were performed in duplicate on two separate occasions when the reaction was linearly dependent upon the protein concentration and time of reaction. Results are expressed as the mean ± SD.

if methoxyflurane is oxidized according to the following hypothetical pathway (14):

```
       Cl  F      H
       |   |      |         cytochrome P-450
  H—C—C—O—C—H    ――――――――――→
       |   |      |            O₂, NADPH
       Cl  F      H

       methoxyflurane
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```
       H          Cl   O
        \         |   //
  2 HF +  C=O + H—C—C
        /         |   \
       H          Cl    OH

  formaldehyde    dichloroacetic acid
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The mechanism that has been proposed (15) for the above reaction is:

```
       Cl  F      H
       |   |      |         cytochrome P-450
  H—C—C—O—C—H    ――――――――――→
       |   |      |            O₂, NADPH
       Cl  F      H
```

```
  ┌    Cl  F      H     ┐
  │    |   |      |     │
  │ H—C—C—O—C—OH  │  →
  │    |   |      |     │
  └    Cl  F      H     ┘
```

```
  ┌   Cl  F    ┐
  │   |   |    │
  │ H—C—C—OH   │   + CH₂O
  │   |   |    │
  └   Cl  F    ┘
```

spontaneously ↓ ↘ HF

```
    Cl  F                  Cl   O
    |   |         H₂O      |   //
  H—C—C=O    ――――――――→  H—C—C      + HF
    |                     |   \
    Cl                    Cl    OH
```

Our results indicate that fluoride ion is a byproduct of the oxidation of methoxyflurane.

The pathway of methoxyflurane metabolism depicted above predicts that dichloroacetic acid is a product of the O-dealkylation. Although we have not yet determined the stoichiometry of dichloroacetic acid production, we have established that it is a product of methoxyflurane biotransformation in rabbit liver microsomes. This has been accomplished by demonstrating that a compound can be extracted from a microsomal reaction mixture which on methylation

has the same retention time in a gas chromatograph (see "Methods") as does an authentic sample of methyl dichloroacetate ($CCl_2HCOOCH_3$). A microsomal reaction mixture that was not exposed to methoxyflurane did not produce this compound. Also, if an authentic sample of dichloroacetic acid was added to a microsomal reaction mixture and the combination was treated as was the sample exposed to methoxyflurane, a product with a retention time identical with methyl dichloroacetate was observed.

The question of whether or not dichloroacetic acid is a metabolite of methoxyflurane metabolism in man has not yet been resolved. In 1970, Holaday and coworkers (14) had reported that dichloroacetic acid was a metabolite of methoxyflurane, but, in a later publication (2), they reported that they were unable to confirm their original observation. As man is known to O-demethylate methoxyflurane, it is likely, especially in view of the data provided in this article, that dichloroacetic acid is a product of the reaction.

It is also revealed in Table 2 that on a molar basis, cytochrome P-450 from rats and rabbits was equally capable of metabolizing methoxyflurane to formaldehyde and fluoride ion, but that rabbit microsomes had a higher concentration of cytochrome P-450 per milligram of microsomal protein.

In order to observe the 2:1 stoichiometric production of fluoride ion and formaldehyde, it was necessary to add EDTA to a final concentration of 1 mM to the rat (but not the rabbit) reaction mixture to inhibit microsomal lipid peroxidation (16). The product(s) of lipid peroxidation interferes with the quantitation of formaldehyde. Lipid peroxidation occurs to a much greater extent in rat liver microsomes because of their relatively high concentration of the polyunsaturated fatty acids that are capable of being peroxidized: arachidonic, docosatetraenoic, docosapentaenoic, and docosahexaenoic acids (16-19). In rats, 30% of the liver microsomal fatty acids consist of these polyunsaturated fatty acids vs 9% in rabbits (18, 19). Formaldehyde is not metabolized by microsomes under our experimental conditions.

In conclusion, although it has been assumed on the basis of indirect evidence that cytochrome P-450 metabolizes methoxyflurane and the other volatile anesthetic agents, no direct proof of this exists to date. The experiments described in this paper contribute critical supportive data to the hypothesis that at least one, but perhaps more, cytochrome P-450 is solely responsible for the O-demethylation of methoxyflurane. Studies with purified, reconstituted cytochrome P-450 are now in progress in our laboratory.

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CLINICAL
reports

Unprecedented Resistance to Neuromuscular Blocking Effects of Metocurine with Persistence after Complete Recovery in a Burned Patient

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Metocurine (mTC), a non-depolarizing muscle relaxant, is a synthetic derivative of d-tubocurarine. Non-depolarizing muscle relaxants such as mTC have become the drugs of choice for skeletal muscle relaxation following burns because of the hyperkalemia and cardiac arrest that can occur following the administration of a depolarizing muscle relaxant such as

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succinylcholine (1). Recently it has been demonstrated that burned patients have higher dose and plasma concentration requirements for non-depolarizing muscle relaxants than nonburned patients to achieve a given degree of skeletal muscle blockade (2, 3). In this communication, we document not only an unprecedented resistance to the neuromuscular blocking effects of mTC in an 8-year-old child with a 35% body surface area burn, but also its persistence for more than 1 year after complete healing of the burn wounds.

Case Report

An 8-year-old boy, having sustained a 35% body surface area burn, was transferred to our institution on the 42nd postburn day. He was markedly asthenic, weighing only 15.5 kg. Surgical excision and grafting of burn wounds were performed on the 50th, 65th, and 72nd postburn days. His burn wounds were completely healed and he was discharged on the 90th postburn day. He was readmitted 13 months later (463 postburn days) for plastic and reconstructive surgery. His anesthetic regimen for the four surgical procedures consisted of thiopental, nitrous oxide/oxygen mixture, and morphine. During these procedures, neuromuscular transmission was studied with Grass FT-03 force displacement transducer. Evoked thumb adduction was recorded in response to a single repeated square wave stimulus applied to the ulnar nerve at the wrist through 22-gauge subcutaneous needles. The electrical impulse was delivered at supramaximal voltage by a Grass S-44 stimulator through a SIU5 isolation unit. The stimulus was 0.2-msec duration, at a rate of 0.1 Hz.

When stable base line twitch recordings were established for 10 to 15 minutes, incremental doses of mTC (0.1 to 0.3 mg/kg) were administered intravenously approximately every 3 minutes until 95% to 98% twitch depression was attained. During recovery of the twitch tension, blood samples were drawn at intervals from a separate venous catheter for measurement of plasma mTC concentration by radioimmunoassay (4). The twitch tension at the time of blood sampling was noted. The time taken for recovery from 5% to 25% of control twitch height was also noted. The magnitude of neuromuscular blockade was calculated as a decrease in twitch height expressed as percentage of control

twitch height. Dose-effect (paralysis) and plasma concentration-effect relationships were plotted on log-probit coordinates. The best-fit line was determined by probit regression (5). ED$_{95}$ and ED$_{50}$ dose and plasma mTC concentrations were derived from each regression line. The dose-effect and the plasma concentration-effect relationships in this patient during the four anesthetics were compared with the mean response of 11 nonburned pediatric surgical patients having the same anesthetic technique.

Results

There was a statistically highly significant $(p <$ 0.01) correlation between dose vs twitch inhibition and plasma mTC concentration vs twitch recovery. The intravenous doses of mTC required for 95% depression of the evoked twitch response were 4.0, 1.6, 1.1, and 0.6 mg/kg on the 50th, 65th, 72nd, and 463rd postburn days, respectively, compared with 0.32 ± 0.02 (SE) mg/kg in control patients. In other words, the dose for 95% twitch depression varied between 2 and 12 times normal. The highest dose was administered at the first excision and grafting procedure. This was followed by a sequential reduction in the dose requirement with time (Figure). One year after complete recovery (463 postburn days), the augmented dose-response curve had not reverted to control values. The administered mTC was well maintained within the circulation throughout the study period, as evidenced by the elevated or normal plasma levels (Table). During administration of the four anesthetics, the plasma concentrations needed for twitch
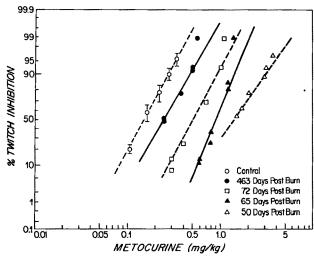
FIGURE. Dose-response curves for each study. Highly significant correlation ($p < 0.01$) was found between intravenous dose and percent twitch inhibition. Control data consisted of nonburned pediatric patients. Although there is gradual decrease in intravenous dose with time, augmented dose requirement had not reverted to normal after 463 days.

depression to 95% of control values varied between 1.25 and 9.6 µg/ml compared with 1.42 ± 0.29 (SE) µg/ml in control patients (Table). The highest plasma concentration was required for the first surgical procedure. The mean times for recovery of twitch tension from 5% to 25% of control twitch height were 29 ± 2 minutes and 28 ± 3.5 minutes in the burned patient and control subjects, respectively. In all four instances, at the end of surgery neuromuscular paralysis was adequately reversed with the usual doses of atropine, 10 to 20 µg/kg, and neostigmine, 25 to 40 µg/kg. There was no evidence of recurarization in the postoperative period.

Discussion

Prior studies (2, 3) have demonstrated that following acute thermal injury non-depolarizing muscle relaxant requirements vary between 2 and 3 times normal. The response of the present patient is different from the mTC response of the burned pediatric patients (3), in that at one stage much higher doses and/ or plasma concentrations of mTC were required and that this difference persisted even at 463 postburn days, which was more than 1 year after complete wound healing. Despite the augmented mTC requirement, the mean time for recovery of twitch tension from 5% to 25% of control values in the present patient was similar to that observed in nonburned patients who received a smaller dose. The higher intravenous dose requirement together with the finding of normal or elevated plasma mTC concentrations for a given twitch suppression suggests end organ resistance rather than altered pharmacokinetics.

In the case of neuromuscular blocking drugs, the relationship between concentration in the body or the intravenous dose on the one hand, and the intensity of the pharmacologic effect on the other hand, can be easily studied clinically by means of the evoked twitch response (6). Using such techniques, it has been demonstrated that patients with myasthenia gravis are extremely sensitive to the non-depolarizing muscle relaxant, d-tubocurarine (7), whereas burned patients are extremely resistant to its effects (2, 3). In the

TABLE

Comparison of Plasma Metocurine Concentrations

	Control	Postburn day			
		50	65	72	463
ED$_{50}$ (µg/ml)	0.72	3.12	0.86	0.71	1.17
ED$_{95}$ (µg/ml)	1.42	9.60	1.36	1.25	3.68

former, the extreme sensitivity is due to a decrease in the number of acetylcholine receptors (7). In burned patients, the basis for the altered response has not been fully characterized. Exudation through the burn wound (8), increased glomerular filtration (9), and altered distribution volume (10) have been suggested as reasons for the increased doses of antibiotics required in these patients. However, as recently shown for d-tubocurarine (11), these factors contribute minimally to the increased muscle relaxant requirement. Altered pharmacokinetics may explain the increased intravenous dose and the duration of action of the drug, but does not explain the elevated plasma level required for a given degree of neuromuscular blockade. Other unknown factors must play a major role in producing the hyposensitivity to non-depolarizing muscle relaxants.

Burned and denervated (hemiplegic, quadriplegic) patients have in common both an exaggerated response to the administration of the depolarizing muscle relaxant succinylcholine (1) and a hyposensitivity to the administration of non-depolarizing muscle relaxants (2, 3, 12-14). Patients with myasthenia, on the other hand, show an attenuated response to succinylcholine (6) and a marked sensitivity to d-tubocurarine (7). Thus, a common mechanism such as a change in numbers of acetylcholine receptors may be the basis for the altered response to both types of muscle relaxants seen in these three groups of patients. In contrast to findings in patients with myasthenia (7), an increase in the number of extrajunctional acetylcholine receptors, which have similar physical and chemical characteristics as junctional receptors, has been found following denervation (15) and immobilization (16). An increase in extrajunctional receptors can increase the sensitivity to acetylcholine (succinylcholine)-induced muscle response (15, 16) and can possibly explain the need for more non-depolarizing muscle relaxant to produce neuromuscular blockade.

The plasma binding of mTC is less than that of d-tubocurarine (17) and the finding of hyposensitivity even to mTC confirms findings in a previous study (17) that increased plasma protein binding of drug is not responsible for the increased plasma requirement of relaxant drugs. The persistence of the hyposensitivity to a non-depolarizing muscle relaxant 1 year after complete recovery (463 postburn days) is unusual and may have another clinical implication. If there is a common etiology, such as an increase in extrajunctional acetylcholine receptors for the altered response to both non-depolarizing and depolarizing muscle relaxant, then it may be speculated that the

hyperkalemic response to a depolarizing muscle relaxant may still be present in completely recovered burned patients even 463 days following burn injury; that is, patients who show a hyposensitivity to non-depolarizing muscle relaxants may show a hyperkalemic response to the administration of depolarizing muscle relaxants. Perhaps the anesthetist should be cautious in the administration of succinylcholine in a burned patient even at this late stage after burn injury.

In summary, by following the indirectly evoked twitch response dose-effect and concentration-effect relationships for metocurine were studied in an 8-year-old burned patient during the acute phase and following 1 year after recovery. Initially, 12 times the normal dose and 8 times the plasma concentration of mTC was required to achieve complete neuromuscular paralysis. The increased dose requirement decreased with time, but persisted even 1 year after complete wound coverage. Hyposensitivity of this magnitude and its persistence so long after injury has not been previously documented and is in contrast to the response of patients with myasthenia gravis. Indirect evidence from the present and previous studies suggest the existence of prolonged changes at the neuromuscular junction in burned patients.

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Hemotherapy during Surgery for Jehovah's Witnesses: A New Method

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We report a hemotherapeutic support procedure used in our institution for Jehovah's Witnesses undergoing major cancer surgery. This involves the preoperative collection of whole anticoagulated blood, its temporary storage in a Haemonetics 30 blood cell processor (H-30), and the simultaneous reinfusion at variable rates in relation to the requirements of the surgical procedures. The extracorporeal blood is thus kept in physical continuity with the circulatory system of the patient at all times.

Case Reports

Case 1

A 19-year-old woman underwent a laparotomy for removal of a large calcified ossifying fibroma of the uterus. Estimated intraoperative blood loss was 3000 to 3500 ml. Total fluid administered was 8250 ml. Hemoglobin and hematocrit values were, respectively, 14.5 g/100 ml and 39.9% before the operation, 6.8 g/100 ml and 20.3% at the lowest point during surgery, and 6.8 g/100 ml and 20% on the 5th postoperative day. Recovery was uneventful.

Case 2

A 46-year-old obese woman (110 kg, 165 cm) with adult onset diabetes mellitus, diabetic peripheral neuropathy, coronary artery disease, and hypertension, underwent a

laparotomy for removal of a large cystic multinodular ovarian mass. Estimated blood loss was 2500 ml, and 5150 ml of crystalloids was administered. Hemoglobin, hematocrit, and platelet count values were 14.5 g/100 ml, 42.4%, and 141,-000/mm³, respectively, before the operation and 8.5 g/100 ml, 25.2% on the 5th postoperative day, respectively, whereas the platelet count reached a low of 106,000/mm³ 2 days after surgery. Due to unexpected bleeding, the lowest hemoglobin and hematocrit values of 7.8 g/100 ml and 23.2%, respectively, were recorded on the 22nd postoperative day. The patient was discharged in satisfactory condition 49 days after surgery.

Methods

Blood is drawn from a catheter inserted into a central vein and connected to the draw-line of a harness fitted to a H-30 (Figure). A 225-ml disposable Latham centrifuge bowl specially designed to separate blood components is used in all cases (1, 2). The blood is anticoagulated with citrate dextrose solution (USP formula B [ACD-B]), added in a ratio of 1:8 at the whole blood draw line. The blood is drawn at a rate of 60 to 80 ml/min. At the completion of the first cycle, approximately 400 ml of blood and plasma is collected and transferred into the in-line reinfusion bag. The reinfusion line is kept patent with a slow infusion rate (50 ml/hr) of 0.9% sodium chloride. The reinfusion bag is connected to two 1000-ml transfer bags to allow a maximum storage of 2000 ml of whole blood. After the first 500 ml of blood has been harvested, maintenance of the circulatory volume is assured by an infusion of Ringer's lactate solution in volumes 2 to 3 times the amount of stored blood.

During surgery, the collected blood is reinfused through a blood administration set with one 170-μ in-line filter at a rate of 10 to 20 ml/hr. Faster reinfusion of blood is performed at a controlled rate of 40 to 50 ml/min. If necessary, the rate can be increased to 150 ml/min without the use of a pressure cuff.

A variation of the technique described (used in case 2), consists of harvesting the platelets at the end of each cycle. At the completion of the procedure, the platelets are extracted from the platelet collection bag, transferred through the in-line connection into the reinfusion bag, and administered.

Anesthetic Management

Anesthetic management is identical with that employed when a hemodilution technique is used. It includes monitoring of direct intra-arterial blood
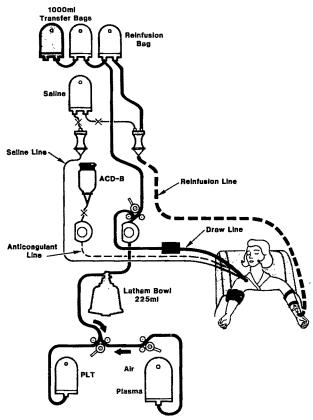
FIGURE. Path used to draw, store, and reinfuse blood in two patients described.

pressure, pulse rate, central venous pressure, pulmonary wedge pressure when indicated, esophageal temperature, hourly urine output, serial determinations of arterial blood gas tensions, hemoglobin, hematocrit, platelet count, prothrombin time, partial thromboplastin time, blood sugar, and electrolytes. In addition, moderate hypothermia to 30 to 32°C is a part of our technique as is controlled hypotension in the absence of contraindications. Ventilation is controlled and anesthesia is maintained with a halogenated anesthetic and oxygen (Fi_{O_2} 1.0).

Discussion

Although some Jehovah's Witnesses accept preoperative collection and storage of their own blood, others find acceptable only a system in which their blood or blood components are not separated from their body and are kept circulating. Various techniques have been devised to comply with these requirements and the idea of major surgery without the

concomitant use of blood or blood substitutes has been accepted in recent years by the medical community (3, 4). The method described above was proposed to the patients and was accepted after consultation with their religious elders.

Although somewhat similar in concept to normovolemic hemodilution (5), the procedure does not interrupt the physical continuity of the blood with the patient (6, 7). The only difference is the presence of the H-30 during the harvesting and storage phases and the ability to store blood components temporarily.

As this method does not involve the collection of blood shed during the surgical procedure, the potential for tumor spread is greatly reduced. Of course, if a patient has tumor cells circulating in his blood, such tumor cells would probably be reinfused. To summarize, the method opens a temporary loop and storage pool in the extra bags attached to the H-30. Although we have not used the device to its full potential, we believe it has a definite advantage in dealing with the problem of major surgery for patients who are Jehovah's Witnesses.

The implications of this new procedure are far-reaching as many patients with acceptable hemoglobin levels who have no objection to blood transfusions sometimes cannot undergo surgery because compatible blood is not available. The procedure could also be used more frequently in patients who do present cross-matching problems, as it eliminates the risk of posttransfusion hepatitis.

Technically, the method is simple, but it requires a close interaction between the anesthesiologist, surgeon, and blood bank physician.

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Succinylcholine in Congenital Pyruvate Kinase Deficiency

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Succinylcholine may cause cardiac arrhythmias and arrest in many pathologic conditions, including patients with burns, tetanus (1), muscle wasting, and upper motor neuron lesions (2). Potasium efflux from muscle and hyperkalemia resulting from succinylcholine-induced depolarization is considered the cause of the arrhythmogenic effects of succinylcholine in such susceptible patients (1).

Congenital pyruvate kinase deficiency, present in 1/20,000 to 40,000 births (3), results in erythrocytes with severe membrane defects associated with extracellular leakage of potassium (3, 4). Three different isozymes of pyruvate kinase exist, although in any one tissue only a single isozyme is present (5). Of the three pyruvate kinase isozymes, one is found predominantly in red blood cells and liver (PK1), another in muscle (PK2), and the third (PK3) in most other tissues. In congenital pyruvate kinase deficiency, only PK1 has been reported to be defective (3).

In view of the known increase in permeability of red cell membranes to potassium in patients with congenital pyruvate kinase deficiency, there is the theoretical possibility that succinylcholine administration might cause hyperkalemia in such patients. No measurements of serum potassium levels associated with succinylcholine administration in individuals with congenital pyruvate kinase deficiency have been published. The following case report documents the course of serial serum potassium values before and after succinylcholine administration in such a patient.

Case Report

A 3½-year-old, 15-kg girl with congenital pyruvate kinase deficiency was admitted for cholesteatoma removal. The patient had received multiple blood transfusions in the past for anemia, and she had had a splenectomy 5 months

previously because of severe anemia resulting from continuing hemolysis.

Before surgery, the patient's serum sodium was 138 meq/L, potassium 4.4 meq/L, chloride 108 meq/L, and bicarbonate 22.7 meq/L. Hematocrit was 33% following transfusion of 1 unit of packed red blood cells.

At 12:13 p.m. on the day of surgery, venous blood (sample 1) was obtained for measurement of serum potassium, ionized and total calcium, pyruvate, and lacatate levels (Table). An intravenous infusion of 5% dextrose in lactated Ringer's solution was begun, and anesthesia induced with thiopental, 50 mg IV, followed by inhalation of halothane and N_2O in O_2. At 12:40 p.m. assisted ventilation at a rate of approximately 30 breaths per minute with a tidal volume of approximately 40 ml was begun, and ventilation was assisted or controlled at approximately this rate and volume for the duration of the procedure.

At 12:45 p.m. succinylcholine, 20 mg IV, was administered and the trachea intubated. Subsequent venous blood samples (Table) were obtained and analyzed as noted above. No cardiac arrhythmias were noted at any time during administration of the anesthetic. The operation was performed without incident, and the patient had an uneventful recovery from anesthesia and surgery.

Discussion

A number of specific enzyme defects in the anaerobic glycolytic pathway of erythrocytes have been identified since 1961, the most common being pyruvate kinase deficiency (6). Enzymatic red cell defects may reflect a generalized defect in other organ systems, as the glycolytic pathway is active in all tissues (3). For example, triose phosphate isomerase deficiency produces not only red cell hemolysis but also muscle and nervous system damage (7).

Pyruvate kinase converts phosphoenolpyruvate to pyruvate, one of the last steps in anaerobic glycolysis. The primary metabolic importance of the pyruvate kinase reaction is the generation of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) (3). The ATP produced is vital for the maintenance of intracellular/extracellular cationic gradients (8), especially potassium (4). In addition, ATP is vital to chelation of ionized calcium by the red cell (3). In pyruvate kinase deficiency, primary abnormalities appear limited to the hematologic system (8), most notably increased permeability of the red cell membrane to potassium (9).

Measurement of serum potassium concentrations (Table) in the patient reported above revealed no marked changes during anesthesia involving sodium thiopental, halothane, N_2O, and succinylcholine. Se-

TABLE

Levels of Serum Potassium, Calcium, Pyruvate, and Lactate in a Patient with Pyruvate Kinase Deficiency*

Sample	Time (p.m.)	K+ (3.6–4.8)	Ca²⁺ (1.8–2.2)	Calcium (9.2–10.8)	Pyruvate (0.3–0.9)	Lactate (5–20)	Comments
1	12:13	3.7	1.97	8.84	0.4	4	Spontaneous vent; awake
2	12:39	3.2	2.02	8.53	0.6	17	Spontaneous vent; anesthetized
3	12:46	3.2	1.95	8.09	0.8	9	Controlled vent; no muscle twitch present; 1 min after succinylcholine
4	12:48	3.3	2.13	8.28	0.7	9	Controlled ventilation
5	1:15	3.2	1.94	8.03	0.4	9	Assisted ventilation
6	1:51	—	—	—	0.3	5	Assisted ventilation
7	2:35	3.3	1.87	8.35	0.5	8	Assisted ventilation

* Normal values are shown in parentheses.

rum potassium concentration, which was normal before anesthesia, increased minimally (0.1 meq/L) following succinylcholine administration.

Although ventilation was controlled or assisted when serum samples were obtained for analysis following succinylcholine administration, marked hyperventilation (which could have decreased serum potassium concentration) was avoided. Thus, any increase in serum potassium levels following succinylcholine in this patient would have been relatively small to have been counteracted by a change due to altered ventilation. Succinylcholine in this patient thus did not appear to cause liberation of a dangerous amount of potassium from muscle. The absence of significant potassium efflux would be expected since, in pyruvate kinase deficiency, only erythrocyte pyruvate kinase (PK1) has been reported to be abnormal (3).

Serum pyruvate and lactate levels were normal before and during anesthesia in the patient described above (Table), although decreased production of erythrocyte pyruvate and lactate would be expected to result from pyruvate kinase deficiency. This suggests that the contribution by erythrocytes to the total circulating pool of pyruvate and lactate is relatively minor.

Finally, serum levels of ionized calcium in this patient remained normal throughout the preoperative and intraoperative period (Table), suggesting that defective red cell chelation of ionized calcium, if present, did not significantly affect total serum ionized calcium content.

In summary, succinylcholine administration in a patient with congenital pyruvate kinase deficiency did not cause hyperkalemia. Succinylcholine use would appear safe in patients with this disease.

ACKNOWLEDGMENT

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letters

letters
TO THE EDITOR

Oxygen Jet Ventilation of Patients with Tracheal T-Tube

To the Editor:

A silicone rubber tracheal T-tube has been proposed by Montgomery (1) as a tracheal stent. Anesthesia and intermittent positive-pressure ventilation (IPPV) of patients having a tracheal T-tube pose a problem as a significant air leak can occur via the upper airway whenever the patient is anesthetized or ventilated via the extraluminal limb of the tube (2, 3). Different procedures have been suggested to prevent the upward air leak, such as occluding the upper airway with a molded polyurethane pharyngeal pack (2) or blocking the upper intraluminal limb of the T-tube with a Fogarty embolectomy catheter (3).

We have successfully used intermittent oxygen jets as an alternative method of IPPV in two women undergoing insertion of tracheal T-tubes. In one patient the T-tube was placed for the management of tracheomalacia following thyroidectomy, whereas in the second patient the tube was placed following surgical excision of excessive tracheal granulations. In both cases, bronchoscopy was initially performed under intravenous thiopental-succinylcholine drip anesthesia, while ventilation was carried out by intermittent oxygen jets (50 psi) delivered via a Sanders Venturi injector adapted to the proximal head of the bronchoscope (4). Jet ventilation was controlled by an electronically operated solenoid switch. After the anatomic diagnosis had been confirmed, surgery proceeded while continuing jet ventilation via the bronchoscope. As soon as the T-tube was placed in the trachea, the bronchoscope was withdrawn and a sterile 2-mm i.d. catheter with one distal hole was advanced via the extraluminal limb of the T-tube into the lower intraluminal limb. Introduction of the catheter was facilitated by gentle upward flexion of the extraluminal limb of the T-tube. The catheter was used as an injector and was directly connected by a high pressure tubing to the electronically controlled solenoid valve (Figure). Ventilation was maintained via the injector catheter by intermittent oxygen jets at a rate of 15/min (I:E 1:3); arterial blood gas analysis during oxygen jet ventilation showed adequate oxygenation and carbon dioxide elimination (Table).

Intermittent oxygen jets can entrain room air and hence minimize or even prevent air leaks during IPPV in patients undergoing tracheobronchial
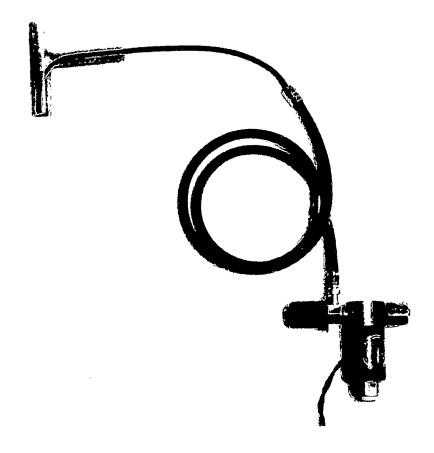
FIGURE. Injector catheter is introduced via extraluminal limb of tracheal T-tube into its lower intraluminal limb. Catheter is connected by high pressure tubing to electronically operated solenoid valve.

TABLE

Arterial Blood Gas Levels before and after 20 Minutes of Intermittent Oxygen-Jet Ventilation

	Preoperative	Intraoperative
Patient 1		
P_{O_2} (mm Hg)	75.0	235.0
P_{CO_2} (mm Hg)	45.0	40.0
pH	7.4	7.42
Patient 2		
P_{O_2} (mm Hg)	95.0	241.0
P_{CO_2} (mm Hg)	36.0	39.0
pH	7.44	7.39

procedures such as bronchoscopy (4), tracheal reconstruction (5), and sleeve pneumonectomy (6). The tracheal T-tube is another cause of air leak that may interfere with conventional IPPV; oxygen jets can therefore be used to ensure adequate ventilation while keeping the unblocked T-tube in situ.

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More on Anesthetic Terminology

To the Editor:

I read with interest the letter by Dr. Deus (1) concerning deletion of the prefix "endo" in terms such as "endotracheal tube," "endotracheal intubation," etc. His point is well taken, but in keeping with his intent one must hope that correct placement of the tracheal tube is monitored using a stethophone.

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REFERENCE

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(Indeed, why not stethophone? Where did stethoscope come from? It came from Laënnec. When in 1819 he introduced his first primitive tube for auscultation of the chest he called it a stethoscope. He did so on the basis that "scope" was derived from the Greek scopos, to examine or observe. Presumably one can examine by listening as well as by looking. That the suffix scope has subsequently been used exclusively to refer to visual examination or observation is perhaps more an indication of how we function medically than an etymologic perversion by Laënnec. Interestingly, in the 1950s the word stethophone was occasionally used but it obviously never achieved appreciable popularity. Ed.)

Transsacral Block

To the Editor:

The review by Simon et al (1), of their results with transsacral block for 15 cases of radiation and interstitial cystitis causing bladder contracture deserves comment, not only to reinforce and extend the use of this important treatment technique for these troublesome conditions, but also to add a note of caution for potentially undesirable effects. These may ensue with less cautious protocols and when other conditions are being treated as in the following two cases:

1. A 54-year-old male addict with complaint of persistent "anal" pain 3 years after abdominoperineal resection, was treated, after bupivacaine trials, with 6% phenol transsacral block. The patient then complained of difficulty with voiding and burning in the area blocked. This patient had previously instituted suit and collected for "malpractice" in connection with his prior surgery. No further blocks were attempted. The patient's complaints about the blocks subsequently subsided.

2. A 29-year-old white woman with pain due to leukemic infiltration of the sacrum was treated with absolute alcohol block at S-3 and S-4 bilaterally after trials with lidocaine. Although good pain relief resulted, this patient developed bladder atony requiring prolonged catheterization. This result contradicted the literature of the time (1954) (2, 3) which cited block of S-3 and S-2 as aiding bladder emptying, and I failed then to appreciate the potential value of the technique for the treatment of bladder contracture.

Aside from these "touchy" examples, we have obtained most gratifying results without adverse side effects in a variety of conditions. Three examples are as follows:

1. A 52-year-old man with radiation cystitis and colitis had announced that suicide was his only option to escape the burden of voiding every 10 minutes, day and night. Treatment with bilateral S-3 phenol blocks produced marked improvement. He returned a few weeks following this treatment with a complaint of some recurrence of frequency. He confided that he had been celebrating over the previous weekend and had "strained himself" by having sexual intercourse approximately 10 times during that period. This recurrence subsided spontaneously. The patient has worked steadily, his relief has persisted, and he has continued to be sexually active for the past 3½ years.

2. A 60-year-old man was responding slowly to treatment with dimethyl sulfoxide for interstitial cystitis. His response improved after several bupivacaine transsacral blocks.

3. A 56-year-old white male schizophrenic in remission complained of long-term perineal "prostate" pain along with some nocturia. He had previously been subjected to two prostatectomies and three transurethral prostatic resections. Block of his right S-3 with bupivacaine and then with phenol effectively eliminated the prostate pain and decreased the frequency.

I hope these comments will serve to emphasize the value and expand the application of the transsacral block technique described so well by Simon et al.

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Tension Pneumoperitoneum

To the Editor:

We would like to call attention to a minor error in word transcription that makes a significant clinical misstatement in our recent report on tension pneumoperitoneum (1). In line 33 (p 147) of the "Discussion," pneumoperitoneum and pneumopericardium are said to "rapidly" follow pneumomediastinum. In fact, unlike subcutaneous emphysema and an occasional pneumothorax, delayed pneumoperitoneum and pneumopericardium *rarely* complicate tracheostomy (2). In the case reported, tension pneumoperitoneum with cardiac arrest occurred after 12 hours of mechanical ventilation and more than 24 hours after tracheostomy. Pneumoperitoneum and pneumopericardium are infrequent, insidious, often catastrophic sequelae of tracheostomy and slowly expanding mediastinal air to which the anesthesiologist should be alert (1, 2).

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Duration of Action of Sodium Citrate as an Antacid

To the Editor:

Aspiration pneumonitis remains a hazard in 16% to 26% of patients during induction of and recovery from anesthesia (1, 2). The administration to adults of the usual doses of anticholinergics in the preoperative medication does not decrease gastric fluid volume or increase gastric fluid pH (3). It is necessary, therefore, especially in high risk patients, to use drugs that will reliably elevate gastric fluid pH. These drugs should also be rapidly acting, have a long duration of action, reduce gastric volume, and be nonparticulate in nature.

Antacids and H_2 inhibitors such as cimetidine are currently used to achieve these goals. Cimetidine, although effective, should be administered at least 45 minutes before induction of anesthesia (4). Sodium citrate (15 ml), a nonparticulate antacid, on the other hand, has been previously shown by us to elevate gastric fluid pH when administered 15 minutes before induction of anesthesia (5).

We recently studied the duration of action of sodium citrate in 10 healthy adult patients undergoing elective nongastric surgery using nitrous oxide and enflurane for anesthesia. Patients received only morphine or meperidine as preoperative medication. Ten minutes before induction of anesthesia each patient was administered 15 ml of 0.3 M sodium citrate. Five milliliters of gastric fluid as aspirated 15, 60, and 180 minutes following induction of anesthesia. The pH of the gastric fluid sample was measured using an analog pH meter (Orion Research model 301). The results of our study revealed the mean gastric fluid pH at 16, 60, and 180 minutes following induction of anesthesia to be 6.0, 5.8, and 5.7, respectively. The gastric fluid pH in all patients except one (pH 2.8) was well above 3.5 even at 3 hours.

The results of our study indicate that 15 ml of 0.3 M sodium citrate is effective in elevating gastric fluid pH for at least 3 hours, during which time most surgical procedures are con-

cluded. This would therefore afford protection against the development of acid pneumonitis should inhalation of gastric fluid occur at the time of extubation of the trachea. Also, the small volume of sodium citrate used minimizes any increase in gastric fluid volume secondary to administration of antacid and would possibly also minimize the severity of aspiration pneumonitis should aspiration occur.

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Butorphanol Anesthesia

To the Editor:

We read with interest the article by Sederberg et al (1) on hemodynamic responses to butorphanol anesthesia in dogs. As the authors stated, butorphanol produces unconsciousness and anesthesia when used for balanced anesthesia, with less respiratory depression than morphine or fentanyl. We have found this to be quite correct, having used butorphanol for the past 5 years both experimentally as well as clinically.

The authors state, after using 0.1-mg and 0.2-mg/kg/min infusions, that higher doses of butorphanol produced cardiovascular depression in their dogs while the animals were breathing oxygen or nitrous oxide-oxygen. They also suggest that butor-

phanol is not a desirable alternative to morphine- or fentanyl-oxygen in the management of patients with severe cardiovascular disease undergoing major operations. Their data may be correct for the animal model used in their study, but we believe they are making a premature and unjustified clinical conclusion. Data resulting from animal experiments cannot always be extrapolated to humans, especially when humans are undergoing surgery, particularly cardiac surgery. We have recently performed a double-blind study in 16 patients undergoing cardiac operations using either butorphanol, 0.15 mg/kg IV, or morphine, 0.75 mg/kg IV, both combined with nitrous oxide-oxygen. Our data (being analyzed for publication) showed no statistically significant differences between the eight patients given butorphanol and the eight patients given morphine in terms of heart rate, mean arterial blood pressure, systemic vascular resistance, mean pulmonary arterial pressure, cardiac index, stroke index, or left or right ventricular stroke work indexes. All of the patients in our study had satisfactory and uneventful anesthesia with either drug. In our study, the two drugs appeared interchangeable in their cardiovascular effect.

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REFERENCE

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book REVIEWS

Obstetric Anesthesia: The Complicated Patient, by F. M. James and A. S. Wheeler, Philadelphia, F. A. Davis Co., 1982, 346 pp, $40.00.

This is not just another textbook on obstetric anesthesia, but a unique compilation of 16 chapters dealing exclusively with complicated obstetrics. Nine chapters are devoted to the more common maternal medical and surgical diseases, one to the febrile parturient (a novel approach), two to the fetus (monitoring, distress), and two to the problems of preterm delivery, breech presentation, and multiple gestation. The final two chapters are concerned with drug addiction and surgery during pregnancy and their effects on mother, fetus, and neonate.

The authors of the various chapters have drawn on their own experience as well as the literature to provide up-to-date, in-depth presentations of their material including pathophysiology, general and obstetric considerations, and recommendations for anesthetic management. Most chapters are highly informative and well referenced. Where controversies exist, more than one opinion is presented.

The design and layout of this book are outstanding. Clearly marked headings and subtitles facilitate finding any desired information without delay. I highly recommend this book for all members of the anesthesia team involved in care of the pregnant woman. After all, almost one third of current deliveries fall into the category of complicated obstetrics.

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Persistent Pain: Modern Methods of Treatment, Volume 3, by S. Lipton and J. Miles, New York, Grune & Stratton, 1981, 260 pp, $48.00.

The preparation of a definitive text on the pathophysiology, diagnosis, and treatment of intractable pain is a frustrating undertaking, as rapid changes in the field render much material obsolete even before publication. Lipton and Miles have found a reasonable alternative to that dilemma by publishing a series of short texts, each limited to a dozen selected topics. This third volume competently reviews and updates a variety of important and often controversial subjects.

I found most of the chapters readable, accurate, and informative. The sections on mechanisms of nociception and pain measurement are concise, understandable, and relevant. The chapter on neural mechanisms of acupuncture is a comprehensive review of the role of endogenous opiates in mediating acupuncture analgesia. Laudably, the author ignores the extensive pseudoscientific literature on the subject.

The short chapter on psychological aspects of chronic pain is refreshingly different from the usual discussion of psychotherapeutic approaches to pain. A separate chapter provides a critical analysis of the potential benefits of biofeedback and relaxation training.

The chapters on statistical analysis of variance, osteoporosis, and endocrine treatment of breast cancer, although competently written, may be of limited appeal and relevance to many readers. I found the "how to" chapters on percutaneous thermal le-

sions, cordotomy, and neurolytic blocks to be the least informative. These latter chapters were generally too cursory to serve as technique manuals and they provided limited information about patient selection or the appropriate role of these modalities in a pain management program.

Overall, there is a good deal of valuable information and insight to be gained from reading this volume. Although its value as a reference is limited, most chapters provide extensive, carefully selected bibliographies. I look forward to reading volume 4.

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Handbook of Critical Care, Second Edition, by J. L. Berk and J. E. Sampliner, Boston, Little, Brown and Co., 1982, 688 pp, $24.50.

The American Board of Medical Specialties has set its seal of approval on the field of critical care medicine by authorizing a Certificate of Special Competence in this specialty for which the first examination is planned in late 1983. A number of texts have appeared to help the trainee on his or her way toward fulfillment of this official goal, and the second edition of this handbook makes a timely appearance among them. The contributors are well qualified to supply authoritative counsel on the applied physiology and supportive management of the catastro-

BOOK REVIEWS

phically ill patient. In general, the information provided is useful for the expert and neophyte alike. As a basic text, it has sound value.

It does, however, have its weaknesses. It is difficult to know why a chapter on oxygen transport, which in itself is well presented, should be included in the section of the book allotted to recent advances in critical care medicine. It is also surprising that an entire chapter in the same section should be devoted to the use of extracorporeal membrane oxygenation, a technique whose time has not yet come and may even have passed, yet there is no mention given to the various forms of high-frequency ventilation now being tested. Perhaps this

omission is explained by the observation that among the seven chapters devoted to recent advances in this field only one chapter has a literature reference later than 1979.

The student will be confused to read on page 95 that "Subjective decisions no longer have a place in the determination of the need for mechanical ventilatory assistance," whereas 70 pages later another author indicates that "The rigid application of criteria based on physiological variables is inappropriate and probably leads to unnecessarily prolonged periods of mechanical ventilation." Some clearer guidance is needed. Not everyone will be as enthusiastic as the text implies about the use of dextrans

for expansion of intravascular fluid volume. These criticisms—and others could be made—may be minor but they are not simply captious, for this second edition emerges at a time when it will be eagerly sought by those training in a new field of medicine, and it has an important role to fill. In a nutshell, this worthwhile book would benefit from disciplined editorial pruning, as it suffers the customary pangs of multiple authorship. The authorship is good, the book is valuable, and it deserves attention.

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References:
1. Bunker, J.P., et al.: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
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Anesthesia and Analgesia

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Anesthesia and Analgesia

Contents

NARCAN⁻ INJECTION
NARCAN⁻ NEONATAL INJECTION (naloxone hydrochloride)
Narcotic Antagonist
Brief Summary of Prescribing Information
INDICATIONS NARCAN is indicated for the complete or partial reversal of narcotic depression, including respiratory depression induced by opioids including natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesics, nalbuphine, pentazocine and butorphanol. NARCAN is also indicated for the diagnosis of suspected acute opioid overdosage
CONTRAINDICATIONS NARCAN is contraindicated in patients known to be hypersensitive to it
WARNINGS NARCAN should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome

The patient who has satisfactorily responded to NARCAN should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN

NARCAN is not effective against respiratory depression due to non-opioid drugs
Usage in Pregnancy: Safe use of NARCAN during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY) However, NARCAN should be administered to pregnant patients only when in the judgment of the physician, the potential benefits outweigh the possible hazards
PRECAUTIONS In addition to NARCAN, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN I V at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN should be used with caution in patients with cardiac irritability

In rare cases, reversal of narcotic anesthesia has resulted in pulmonary edema
ADVERSE REACTIONS Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness. In postoperative patients, excessive dosage of NARCAN may result in significant reversal of analgesia and excitement. In some cardiac patients, the resultant hypertension and tachycardia may result in left ventricular failure and pulmonary edema. In the absence of narcotics naloxone is essentially devoid of side effects
DOSAGE AND ADMINISTRATION NARCAN (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations

Since the duration of action of some narcotics may exceed that of NARCAN the patient should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary
USAGE IN ADULTS Narcotic Overdose — Known or Suspected: The usual initial adult dose is 0 4 mg (1 ml) NARCAN administered I V I M or S C If the desired degree of counteraction and improvement in respiratory function is not obtained immediately following I V administration, it may be repeated intravenously at 2 to 3 minute intervals Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs
Postoperative Narcotic Depression: For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN are usually sufficient The dose of NARCAN should be titrated according to the patient's response For the initial reversal of respiratory depression, NARCAN should be injected in increments of 0 1 to 0 2 mg intravenously at two to three minute intervals to the desired degree of reversal, i e , adequate ventilation and alertness without significant pain or discomfort Excessive dosage of NARCAN may result in significant reversal of analgesia and increase in blood pressure Similarly, too rapid reversal may induce nausea, vomiting, sweating or circulatory stress

Repeat doses of NARCAN may be required within one to two hour intervals depending upon the amount, type (i e short or long acting) and time interval since last administration of narcotic Supplemental intramuscular doses have been shown to produce a longer lasting effect
USAGE IN CHILDREN Narcotic Overdose — Known or Suspected: The usual initial child dose is 0 01 mg kg body weight given I V I M or S C This dose may be repeated in accordance with the adult administration guideline If necessary, NARCAN can be diluted with sterile water for injection
USAGE IN NEONATES Narcotic-induced depression: The usual initial dose is 0 01 mg kg body weight administered I V I M or S C This dose may be repeated in accordance with adult administration guidelines
HOW SUPPLIED 0 4 mg ml of NARCAN (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration Available as follows

1 ml ampuls in boxes of 10	NDC 0590-0365-10
1 ml disposable prefilled syringes	
boxes of 10	NDC 0590-0365-15
boxes of 25	NDC 0590-0365-25
10 ml vials	NDC 0590-0365-05

0 02 mg ml of NARCAN (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration. Available as

2 ml ampuls in boxes of 10	NDC 0590-0367-10

6108-2
NARCAN is a registered U S trademark of Endo Pharmaceuticals, Inc

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(chloroprocaine hydrochloride)

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(chloroprocaine hydrochloride)

Nesacaine®-CE
(chloroprocaine hydrochloride)

BRIEF SUMMARY:
Nesacaine, in multidose vials with preservative, is indicated for the production of local anesthesia by infiltration and regional nerve block; it should not be used for caudal or epidural anesthesia.

Nesacaine-CE, in single dose vials without preservative, is indicated for the production of local anesthesia by infiltration and regional nerve block, including caudal and epidural blocks.

Contraindications: hypersensitivity to drugs of the PABA ester group; central nervous system disease is a contraindication to caudal or epidural block.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage In Pregnancy: Safe use of chloroprocaine HCl has not been established with respect to adverse effects upon fetal development. This fact should be carefully considered before administering the drug to women of childbearing potential, particularly during early pregnancy.

Obstetrical Paracervical Block: Chloroprocaine is not recommended for obstetrical paracervical block when toxemia of pregnancy is present or when fetal distress or prematurity is anticipated in advance of the block. Fetal bradycardia has been noted by electronic monitoring in about 5-10% of the cases where initial doses of 120 mg to 140 mg of chloroprocaine were used. The incidence of bradycardia, within this dose range, might not be dose related. These data are limited and are generally restricted to non-toxemic cases where fetal distress or prematurity was not anticipated in advance of the block. The role of drug factors and non-drug factors associated with fetal bradycardia following paracervical block are unexplained at this time.

In obstetrics, some oxytocic drugs may cause severe persistent hypertension if vasoconstrictor drugs are used to correct hypotension or are added to the local anesthetic solution.

Solutions containing vasoconstrictors, particularly epinephrine and norepinephrine, should be used with extreme caution in patients receiving MAO inhibitors and tricyclic antidepressants, since severe prolonged hypertension may occur.

Precautions: The safety and effectiveness of chloroprocaine HCl depends upon proper dosage, correct technique, adequate precautions and readiness for emergencies.

Solutions containing vasoconstrictors should be used cautiously in the presence of disease which may adversely affect the patient's cardiovascular system, in areas where the blood supply is limited, or when peripheral vascular disease is present.

Injections should always be made slowly and with frequent aspiration to avoid inadvertent rapid intravascular administration which can produce systemic toxicity.

Serious cardiac arrhythmias may occur if preparations containing a vasopressor are used in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other related agents.

Adverse Reactions: Systemic adverse reactions result from high plasma levels due to rapid absorption, inadvertent intravascular injection, excessive dosage, hypersensitivity, idiosyncrasy, or diminished tolerance. Central nervous system reactions: excitation and/or depression; restlessness, anxiety, dizziness, blurred vision, or tremors, possibly proceeding to convulsions. Depression may be the first manifestation followed by drowsiness merging into unconsciousness and respiratory arrest.

Cardiovascular system reactions: depression of the myocardium manifested by an initial episode of hypotension, bradycardia, and cardiac arrest.

Neurologic adverse reactions: In the practice of epidural block, occasional inadvertent penetration of the subarachnoid space may occur; subsequent reactions may include spinal block of varying magnitude, loss of bowel and bladder control, loss of perineal sensation and sexual function. Persistent neurological deficit of some lower spinal segments with slow recovery (several months) has been reported in rare instances.

Dosage and Administration: See full prescribing information.

NESACAINE is supplied in 1% and 2% solutions in 30 ml multiple dose vials:

NESACAINE-CE is supplied in 2% and 3% solutions in 30 ml single dose vials.

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This new technique helps prevent sympathetic breakthrough and all the problems that stem from "chasing the patient."

3. Permits most patients to breathe spontaneously at completion of surgery*

4. Reduces need for postoperative narcotics

Postoperatively, residual plasma and tissue levels provide sufficient analgesia to minimize the need for additional narcotics.

Available in easy-to-use 10 ml ampoules

Pharmacokinetics of a single I.V. dose of 6.4 µg/kg fentanyl base in man[1]

ng/ml of Plasma vs. Hours after injection

Slightly depressed spontaneous respiration below 1.5 ng/ml; normal respiration below 0.7ng/ml.[1]

*****Note:** Respiratory depression may last longer than analgesic action and this risk increases with increasing doses.

1. McClain DA and Hug CC, Jr.: Intravenous fentanyl kinetics. *Clin Pharmacol Ther* 28(1): 106-114, 1980.

Please see brief summary of Prescribing Information on next page.

Sublimaze®
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Protect from light. Store at room temperature.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY
DESCRIPTION
Each ml. contains:

Fentanyl .... 50 mcg. (0.05 mg.) as the citrate

Warning: May be habit forming.

Sodium hydroxide for adjustment of pH to 4.0-7.5.

CONTRAINDICATIONS
SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS
AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATION EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA. See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition. Where moderate or high doses are used (above 10 mcg./kg.), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received SUBLIMAZE (fentanyl). It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Drug Dependence—SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure—SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children—The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy—The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects, therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS
The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression or doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of SUBLIMAZE (fentanyl) are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol) hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol).

When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS
As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with *INAPSINE* (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION
50 mcg. = .05 mg. = 1 ml.

Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

I. *Premedication*—Premedication (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly 30 to 60 minutes prior to surgery.

II. *Adjunct to General Anesthesia*—See Dosage Range Chart

III. *Adjunct to Regional Anesthesia*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

IV. *Postoperatively (recovery room)*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usual Children's Dosage: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 20 to 30 mcg. (0.02 to 0.03 mg.)(0.4 to 0.6 ml.) per 20 to 25 pounds is recommended.

DOSAGE RANGE CHART

> **TOTAL DOSAGE**
>
> **Low dose**—2 mcg./kg. (.002 mg./kg.) (.04 ml./kg.) SUBLIMAZE* injection. Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period. *Maintenance*: Additional dosages of SUBLIMAZE* injection are infrequently needed in these minor procedures.
>
> **Moderate dose**—2-20 mcg./kg. (.002-.02 mg./kg.)(.04-0.4 ml./kg.) SUBLIMAZE* injection. Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential. *Maintenance*: 25 to 100 mcg. (0.025 to 0.1 mg.)(0.5 to 2.0 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.
>
> **High dose**—20-50 mcg./kg. (.02-.05 mg./kg.)(0.4-1 ml./kg.) SUBLIMAZE* injection. During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20-50 mcg./kg. (.02-.05 mg.)(0.4-1 ml.) of SUBLIMAZE* injection with nitrous oxide oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH, and prolactin.
>
> When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression.
>
> The main objective of this technique would be to produce "stress free" anesthesia. *Maintenance*: Maintenance dosage (ranging from 25 mcg. (.025 mg.)(0.5 ml.) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

As a General Anesthetic
When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg./kg. (.05 to 0.1 mg./kg.)(1 to 2 ml./kg.) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg./kg. (.15 mg./kg.)(3 ml./kg.) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

OVERDOSAGE
Manifestations: The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; and oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

HOW SUPPLIED
2 ml. and 5 ml. ampoules—packages of 10.
NDC 50458-030-02 **NDC** 50458-030-05

10 ml. and 20 ml. ampoules—packages of 5.
NDC 50458-030-10 **NDC** 50458-030-20
(For intravenous use by hospital personnel specifically trained in the use of narcotic analgesics)

March, 1980. Revised June, 1980. January, 1981

U.S. Patent No. 3, 164 600

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The VSM 1 Vital Signs Monitor from Physio-Control.

KIT

A sterile, disposable, prefilled syringe and cannula kit for convenient laryngotracheal anesthesia prior to intubation, diagnosis, surgery.

25% more drug than other kits*
- contains 5ml Xylocaine® (lidocaine HCl) 4% Solution to allow for greater range of dosage determination

Calibrated barrel
- marked in 1/2 ml increments to aid in proper dose determination and accuracy of drug delivery

Prefilled syringe
- totally sterile and self-contained
- no vial to insert, no risk of contamination

Hub guard
- a simple twist quickly activates the syringe and readies the unit for attachment of cannula or needle

Luer hub
- firmly secures needle or cannula

Safety strap
- an extra precaution against inadvertent cannula disengagement

Separate syringe unit
- lets you choose either intraoral or transtracheal routes of administration at your discretion

Cannula
- anatomically curved to facilitate introduction into larynx and trachea.
- easily attaches to syringe, virtually no assembly time

*Although absorption of lidocaine from respiratory mucosa varies widely among individuals, blood concentrations achieved by this route can rise to levels comparable to those reached by similar doses infused intravenously, and in some cases almost as rapidly.[1,2,3]

REFERENCES
1. Bromage P: Concentrations of lidocaine in the blood after intravenous and endotracheal administration. Anaesthesia, 16:461, 1961.
2. Chu S: Plasma concentration of lidocaine after endotracheal spray. Anesth. Analg., 54:438, 1975.
3. Pelton D: Plasma lidocaine concentrations following topical aerosol application to the trachea and bronchi. Canad. Anaesth. Soc. J., 17:250, 1970.

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(Please see following page for a brief summary of prescribing information.)

For one of medicine's most demanding skills... one of medicine's most dependable agents

Ethrane®
(enflurane)

precise control...stability of heart rhythm...
reduced relaxant requirement...prompt, smooth recovery
...organ toxicity rare or nonexistent

Ethrane 10 years of experience confidence safety
(enflurane)

Ohio Medical Anesthetics

Ēthrane® (enflurane)

CAUTION Federal Law Prohibits Dispensing without a Prescription

DESCRIPTION

ĒTHRANE (enflurane) (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether) (CHF_2OCF_2CHFCl) is a nonflammable inhalation anesthetic agent. The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation.

$$\log_{10}P = A + B/T \qquad \begin{aligned} A &= 7.967 \\ B &= -1678.4 \\ T &= °C + 273.16 \text{ (Kelvin)} \end{aligned}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20°C is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C.

Enflurane is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary even in the presence of ultraviolet light. Enflurane is stable to strong base and does not decompose in contact with soda lime and does not react with aluminum, tin, brass, iron or copper. The partition coefficients of enflurane at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ĒTHRANE (enflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70 percent nitrous oxide—30 percent oxygen, and 1.17 in 30 percent nitrous oxide—70 percent oxygen.

Induction and recovery from anesthesia with enflurane are rapid. Enflurane has a mild, sweet odor. Enflurane may provide a mild stimulus to salivation or tracheobronchial secretions. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia can be changed rapidly by changing the inspired enflurane concentration. Enflurane reduces ventilation as depth of anesthesia increases. High $PaCO_2$ levels can be obtained at deeper levels of anesthesia if ventilation is not supported. Enflurane provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during enflurane anesthesia. Enflurane anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with enflurane and injected with epinephrine containing solutions to achieve hemostasis in a highly vascular area (transsphenoidal surgery), it is recommended that 2 micrograms per kilogram (2 µg/kg) of epinephrine may be injected subcutaneously over a 10 minute period. This may be repeated up to 3 times per hour.

Example: Up to 10 ml of 1:100,000 epinephrine containing solution (10 µg/ml) may be injected subcutaneously over a 10 minute period in a 50 kilogram patient judged to have ordinary tolerance to epinephrine administration. No more than 30 ml of 1:100,000 epinephrine containing solution (10 µg/ml) should be administered to such a patient per hour. The concomitant administration of lidocaine enhances the safety of the use of epinephrine during enflurane anesthesia. This effect of lidocaine is dose related. All customary precautions in the use of vasoconstrictor substances should be observed.

Example Two: Alternatively, up to 20 ml of 1:200,000 epinephrine containing solution (5 µg/ml) may be substituted for 10 ml of 1:100,000 solution in the above example.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with enflurane. The NON-DEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of enflurane.

Biotransformation of enflurane in man results in low peak levels of serum fluoride averaging 15 µM/L. These levels are well below the 50 µM/L threshold level which can produce minimal renal damage in normal subjects. However, patients chronically ingesting isoniazid or other hydrazine containing compounds may metabolize greater amounts of enflurane. Although no significant renal dysfunction has been found thus far in such patients, peak serum fluoride levels can exceed 50 µM/L, particularly when anesthesia goes beyond 2 MAC hours. Depression of lymphocyte transformation does not follow prolonged enflurane anesthesia in man in the absence of surgery. Thus enflurane does not depress this aspect of the immune response.

Enflurane 0.25 to 1.0 percent (average 0.5 percent) provides analgesia equal to that produced by 30 to 60 percent (average 40 percent) nitrous oxide for vaginal delivery. With either agent, patients remain awake, cooperative, and oriented. Maternal blood losses are comparable. These clinical approaches produce normal Apgar scores. Serial neurobehavioral testing of the newborn during the first 24 hours of life reveals that neither enflurane nor nitrous oxide analgesia is associated with obvious neurobehavioral alterations. Neither enflurane nor nitrous oxide when used for obstetrical analgesia alters serum BUN, creatinine, uric acid or osmolality. The only difference in the use of these two agents for obstetrical analgesia appears to be higher inspired oxygen concentration that may be used with enflurane.

Analgetic doses of enflurane, up to approximately 1 percent, do not significantly depress the rate or force of uterine contraction during labor and delivery. A slowing of the rate of uterine contraction and a diminution of the force of uterine contraction is noted between the administration of 1 and 2 percent delivered enflurane; concentrations somewhere between 2 and 3 percent delivered enflurane may abolish uterine contractions. Enflurane displaces the myometrial response curve to oxytocin so that at lower concentrations of enflurane oxytocin will restore uterine contractions; however, as the dose of enflurane progresses (somewhere between 1.5 and 3 percent delivered enflurane) the response to oxytocin is diminished and then abolished. Uterine bleeding may be increased when enflurane is used in higher concentrations for vaginal delivery or to facilitate delivery by Cesarean section; however, this has not been demonstrated within the recommended dosage range (see DOSAGE AND ADMINISTRATION section). Mean estimated blood loss in patients anesthetized for therapeutic abortion with 1 percent enflurane in 70 percent nitrous oxide with oxygen is approximately twice that noted following therapeutic abortion performed with the use of a local anesthetic technique (40 ml versus 20 ml).

INDICATIONS AND USAGE

ĒTHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Enflurane may be used to provide analgesia for vaginal delivery. Low concentrations of enflurane (see DOSAGE AND ADMINISTRATION) may also be used to supplement other general anesthetic agents during delivery by Cesarean section. Higher concentrations of enflurane may produce uterine relaxation and an increase in uterine bleeding.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).
Known sensitivity to ĒTHRANE (enflurane) or other halogenated anesthetics.
Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Increasing depth of anesthesia with ĒTHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentrations usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged enflurane anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to depth of anesthesia. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

PRECAUTIONS

The action of nondepolarizing relaxants is augmented by ĒTHRANE (enflurane). Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from neuromuscular blockade will be longer in the presence of enflurane than when halothane or nitrous oxide with a balanced technique are used.

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. Enflurane should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug.

In susceptible individuals, enflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) The syndrome of malignant hyperthermia secondary to enflurane appears to be rare; by March 1980, 35 cases had been reported in North America for an approximate incidence of 1/725,000 enflurane anesthetics.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuation of triggering agents (e.g., enflurane), administration of intravenous dantrolene, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. Renal failure may appear later, and urine flow should be sustained if possible.

Swiss ICR mice were given enflurane to determine whether such exposure might induce neoplasia. Enflurane was given at ½, ⅛, and ¹⁄₃₂ MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice who were given the same background gases, but not the anesthetic.

Exposure of mice to 20 hours of 1.2 percent enflurane causes a small (about ½ of 1%) but statistically significant increase in sperm abnormalities. In contrast to these results, in vitro approaches to the study of mutagenesis (Ames test, sister chromatid exchange test, and the 8-azaguanidine system) have not shown a mutagenic effect of enflurane.

Pregnancy Category B:
Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to enflurane. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

ADVERSE REACTIONS

1. Malignant hyperthermia
2. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ĒTHRANE (enflurane) anesthesia, or light levels with hypocapnia.
3. Hypotension and respiratory depression have been reported.
4. Arrhythmias, shivering, nausea, and vomiting have been reported.
5. Elevation of the white blood count has been observed.

OVERDOSAGE

In the event of overdosage, the following action should be taken:
Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

The concentration of ĒTHRANE (enflurane) being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using
a) vaporizers calibrated specifically for enflurane;
b) vaporizers from which delivered flows can easily and readily be calculated.
Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by enflurane and that enflurane does not alter heart rate. The use of anticholinergic drugs is a matter of choice.
Surgical Anesthesia: Induction may be achieved using enflurane alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the enflurane mixture. In general, inspired concentrations of 2.0-4.5 percent enflurane produce surgical anesthesia in 7-10 minutes.

Surgical levels of anesthesia may be maintained with 0.5-3 percent enflurane. Maintenance concentrations should not exceed 3 percent. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of enflurane concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Analgesia: Enflurane 0.25 to 1.0 percent provides analgesia for vaginal delivery equal to that produced by 30 to 60 percent nitrous oxide. These concentrations normally do not produce amnesia. See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section.

Cesarean Section: Enflurane should ordinarily be administered in the concentration range of 0.5 to 1.0 percent to supplement other general anesthetics. See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section.

HOW SUPPLIED

ĒTHRANE (enflurane) is packaged in 125 and 250 ml amber-colored bottles.

Ēthrane® (enflurane) **10** years of experience confidence safety

Ohio Medical Anesthetics

When patients would rather <u>not</u> remember...

ATIVAN® (LORAZEPAM) Ⓥ
INJECTION IM or IV

DESCRIPTION: Ativan® (lorazepam) Injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal failure. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two breeds of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately post-injection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure. Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure. EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

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MARK YOUR CALENDAR NOW—PLAN TO ATTEND THIS IMPORTANT CONTINUING MEDICAL EDUCATION ACTIVITY

EDITORIAL

Advanced CPR—Student, Teacher, Administrator, Researcher

Socrates was a man.
Socrates was a Greek.
Socrates went around
telling people what to do.
They poisoned him!

SUCH WAS the biography of the great teacher, penned by a 5th grade student. It is, therefore, with some trepidation, and a certain degree of humility, that we would like to suggest that you (yes we do mean *all of you*) consider taking a formal course in Advanced Cardiac Life Support (ACLS)-Cardiopulmonary Resuscitation (CPR). Why do many anesthesiologists resist such training? What is the rationale behind our recommendation?

The anesthesiologist who rejects the instructor who encourages participation in ACLS-CPR education often justifies his or her unwillingness to study ACLS by expressing amazement at the implication of a need to learn what he or she already knows (1). Inducing the anesthetic state and maintaining viability of the patient appears to be the anesthesiologist's daily demonstration of his or her knowledge and skill in the procedures of ACLS. Who better combines the techniques of airway management, fluid and pharmacologic manipulation, cardiovascular monitoring, and cardiac and cerebral preservation?

We do not dispute the anesthesiologists' expertise in life support in the operating room. Answer several questions, however, before you are sure you are knowledgeable and skillful enough to provide ACLS-CPR in all possible settings. How will you treat the person who has a foreign body airway obstruction the next time you are at a fast-food restaurant? What will you do with the defibrillator paddles handed to you by the paramedic, during a cardiac resuscitation you volunteered to help in while watching a professional baseball game? Which drugs, and in what doses, will you prescribe for the 4-year-old child being resuscitated at the lake after a drowning accident? If you have the answers to all of the questions like these, do not read anymore of this plea.

We believe that anesthesiologists' knowledge of and skill in ACLS-CPR can be improved. There is evidence to support this statement. Our survey of the members of one American Society of Anesthesiologists component society indicated that most (74%) had read the current ACLS-CPR literature but few (21%) had ever taken a course (2). When quizzed on the factual aspects of ACLS, the surveyed anesthesiologists who had never taken a course scored only 55% correct answers. Knowledge score on individual items varied greatly. For example, only 32% correctly cited the defibrillation dose range for a 20-kg child. Because they do not use defibrillators on a daily basis, anesthesiologists may forget the correct dose range to best treat an arrest victim and minimize complications. Although anesthesiologists may be expert in many areas of life support, they have obvious deficiencies in the body of knowledge encompassed in the American Heart Association ACLS course.

The situation for life-support skills is no better. When we assessed a 1st year anesthesia resident class performing ACLS-CPR psychomotor skills, similar problems were identified (3). A 55% deficiency existed in spite of the fact that this group represented recent medical school graduates, most with 1 postgraduate year of clinical experience which frequently included involvement in resuscitation and life support. Although residency training will definitely correct the problems we observed with routine airway management, it is doubtful that skill training and testing on the use of the esophageal obturator airway, oxygen-powered mechanical breathing devices, defibrillators, automatic chest compressors, or Military Anti-Shock Trousers (M.A.S.T.) will be conducted unless specifically provided for in the anesthesia residency curriculum.

Rendering life support in the controlled, nonemergency, operating room environment is quite different from the cardiac arrest situation. Events transpire within seconds to minutes during an arrest, whereas a longer time frame, often with relatively gradual

changes, is more often the case during anesthesia. Rapid, efficient, almost reflex behaviors are required during resuscitation to maximize a victim's chances for functional survival. Little time exists during a cardiac arrest for cogitation on drug doses or arrhythmia recognition, or for fumbling to set up and use a piece of equipment. No time exists for specialists to be summoned to "do their thing." Several studies have recently documented that correct institution of ACLS-CPR procedures within approximately 8 minutes of the initiation of the cardiac arrest dramatically improves prognosis (4, 5). In many instances, it is the responsibility of the one or two "experts" present to direct and deliver all aspects of ACLS-CPR care.

Anesthesiology has been defined as a discipline that includes that responsibility. The American Board of Anesthesiology states in its *Booklet of Information* that anesthesiology is a practice including ". . . The clinical management and teaching of cardiac and pulmonary resuscitation . . ." (6). The United States Department of Labor defines our specialty in similar terms (7). Most recently, the Joint Commission on Accreditation of Hospitals (JCAH) redefined its position on CPR education. The JCAH now places the anesthesiologist in a position of authority with respect to both CPR care and education (8). These definitions, and the expectations of others inherent in them, define a role for the anesthesiologist, and support our contention that anesthesiologists need ACLS-CPR education. In addition to providing a standard of care, anesthesiologists are expected to teach others that standard, and to organize, coordinate, and provide the delivery of both CPR care and education. An incidental benefit from an active ACLS-CPR educational role is the more widespread visibility of anesthesiologists and potential recruiting ability for our specialty.

A final justification for encouraging anesthesiologists to expose themselves to formalized ACLS-CPR training concerns resuscitation research. Many of the "standard" ACLS-CPR therapies accepted today have been promulgated from common sense, logic, anecdote, or scientific best guess. The recent studies that have been conducted to provide more scientific data only came about because somebody knew what was accepted as standard care and dared to question its

validity. Only after anesthesiologists have read and actively learned the "book," are they in a position to query what is the "gospel."

ACLS-CPR clinical care, teaching, administration, and research are all activities applicable to anesthesiologists. Involvement in any or all of these activities clearly justifies our belief that anesthesiologists need ACLS-CPR training. We as teachers, however, do not dictate policy. Teachers make statements to engage students in a process of thought, consideration, and review. It is you, the pupil, who finally accepts or rejects the concept, in this instance, our recommendation that anesthesiologists need to and should learn ACLS.

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Factors Associated with Perioperative Complications during Carotid Endarterectomy

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ASIDDAO, C. B., DONEGAN, J. H., WHITESELL, R. C., AND KALBFLEISCH, J. H.: Factors associated with perioperative complications during carotid endarterectomy. Anesth Analg 1982;61:631-7.

Records from 166 cases of unilateral carotid endarterectomy were reviewed to investigate the association of certain preoperative and intraoperative factors with perioperative complications including hypertension and hypotension, neurologic deficit, myocardial infarction, and mortality. No myocardial infarctions occurred and mortality was zero. Complications associated with some of the study factors included postoperative hypertension and neurologic deficit. Postoperative hypertension occurred more frequently (a) in patients with poor preoperative blood pressure (BP) control (BP ≥ 170/95 torr) than in those with adequate control (BP < 170/95 torr) or normotension (52%, 35%, and 17%, respectively, $p < 0.01$) and, (b) when additional peripheral vascular disease was present (43% vs 25%, $p < 0.05$). The incidence of neurologic deficit was higher when hypertension developed after surgery (20%) than when patients remained normotensive (6%) or developed hypotension (0%, $p < 0.05$). Patients whose hypertension was poorly controlled had a greater incidence of transient neurologic deficit (23.8%) than patients with controlled hypertension (2.5%) or patients with normotension (1.5%, $p < 0.01$); permanent neurologic deficit occurred more frequently in those with bilateral disease on angiography than in those with unilateral disease (8.8% vs 1.2%, $p < 0.05$).

Key Words: SURGERY: carotid endarterectomy; BRAIN: carotid endarterectomy.

INDIVIDUALS with mild to moderate hypertension tolerate anesthesia and surgery without significant cardiovascular complications (1, 2), whereas those with untreated or inadequately treated hypertension frequently develop intraoperative hypotension and myocardial ischemia (2). This study examined the operative and postoperative course of a group of patients with a high incidence of hypertension and frequent occurrence of intraoperative and postoperative blood pressure lability, i.e., those undergoing carotid endarterectomy.

Postoperative blood pressure lability frequently oc-

curs following carotid endarterectomy (3-8) and may be associated with an increased incidence of neurologic complications (4, 8). The exact reason for this lability is not completely understood, but the presence of preoperative hypertension may be a contributing factor (7, 8). Other causes which have been suggested include altered baroreceptor activity (3, 5-7) and abnormal plasma volume (5).

Control of blood pressure significantly reduces mortality and morbidity in hypertension (9, 10), including the prevention or delay of initial or recurrent stroke (11, 12). In the present study, the relationship of adequate preoperative control of hypertension to the incidence of intraoperative and postoperative blood pressure lability, neurologic deficit, myocardial infarction, and operative mortality was examined.

Several other preoperative and intraoperative factors, including coexistent medical problems, presenting neurologic symptoms, extent of carotid artery disease, type of anesthetic, use of an intra-arterial catheter, and use of an indwelling shunt were also evaluated to determine their relationship to perioperative complications.

Methods

Selection of Patients

The records for all carotid endarterectomies performed at the Milwaukee County Medical Complex from December 19, 1972 to September 17, 1980 were reviewed. Patients with prior contralateral carotid surgery or simultaneous coronary artery bypass were excluded. The resulting series consisted of 166 cases.

Study Factors

Medical records were examined for information pertaining to preoperative, intraoperative, and postoperative periods. The postoperative period was defined as the time from the patient's arrival in the recovery room until discharge from the hospital.

Variables coded from the hospital records included: (a) preoperative blood pressure; (b) anesthetic agent(s); (c) coexistence of diabetes mellitus, heart disease, or other peripheral vascular disease; (d) presenting neurologic manifestations (e.g., asymptomatic bruit, transient ischemic attack, previous stroke, other symptoms); (e) angiographic description of carotid artery disease (i.e., ipsilateral or bilateral, <50% or ≥50% occlusion, presence or absence of intra-arterial ulcers); (f) use of an inlying shunt; (g) use of direct arterial blood pressure monitoring; (h) duration of anesthesia and surgery; and (i) perioperative complications.

Preoperative systolic and diastolic blood pressures recorded following hospital admission were averaged. Patients without a history of hypertension, whose systolic pressure averaged less than 160 torr and diastolic pressure less than 95 torr, were considered normotensive. Patients receiving medical treatment for hypertension were considered controlled hypertensives if their average blood pressure was less than 170 torr systolic and 95 torr diastolic. Patients with a systolic pressure ≥ 170 torr and/or diastolic pressure ≥ 95 torr were considered poorly controlled hypertensives. Patients without a history of hypertension, but whose averaged preoperative blood pressure fell in the latter category, were grouped with the poorly controlled hypertensives.

All procedures were performed under general anesthesia. The anesthetic technique was classified as the following: (a) inhalation (nitrous oxide supplemented by halothane or enflurane, (b) balanced (nitrous oxide supplemented by morphine, meperidine, or fentanyl and a muscle relaxant), or (c) combination (nitrous oxide-narcotic supplemented with halothane

or enflurane). The total cumulative dose of thiopental received by the patient up to the time of carotid artery clamping was coded as high (15 mg/kg), low (4 to 10 mg/kg), or none (another induction agent used).

Postoperative events studied were: (a) hypertension and hypotension, (b) transient or permanent neurologic complications, (c) myocardial infarction, and (d) mortality. Intraoperative as well as postoperative hypertension was defined as a sustained increase in systolic blood pressure to ≥200 torr and/or diastolic pressure to ≥110 torr requiring pharmacologic control. Intraoperative or postoperative hypotension was considered to have occurred when a vasopressor was necessary to maintain systolic blood pressure within 10% of the upper range of preoperative levels. Neurologic complications were divided into permanent or transient deficits depending on whether new cerebral ischemic manifestations observed following carotid endarterectomy persisted for more than 24 hours.

Statistical Methods

Evaluation of the influence of medical history, anesthesia, and the other aforementioned categorical study variables on perioperative complications was accomplished by log-linear multidimensional contingency table analysis (13). Study factors were judged to be related if the corresponding interaction term in the log-linear model was declared significant with tests of partial and marginal association. To display the results, the data are presented as percentages in tabular form so that the relation or lack of relation between a study variable and complication can be seen. Differences in mean values of continuous study variables were assessed with analysis of variance and multiple comparison techniques (14). In all statistical testing, probability levels of 0.05 and 0.01 were used for significance.

Results

In this series of 166 patients, 55% were male and 45% female. The mean age was 63 years. Diabetes mellitus was present in 26% of the patients and other peripheral vascular disease in 28%. Heart disease as determined by history, electrocardiography, or cardiac catheterization was evident in 57% of the patients.

In 83% of the patients direct intra-arterial pressure monitoring was utilized. All patients were mechanically ventilated and arterial P_{CO_2} was kept normal for the individual. An inlying shunt was used in 79% of the cases. Mean anesthesia time was 186.3 ± 40.8 (SD) minutes; mean operating time was 138.29 ± 38.4 minutes.

Thirty-seven percent of patients required a vaso-pressor to maintain intraoperative systolic blood pressure within approximately 10% of the upper range of the preoperative levels. Phenylephrine was used in 58 of the 61 total cases. The occurrence of intraoperative hypotension was not influenced by the presence of heart disease (Table 1). A higher incidence of intraoperative hypotension was seen in hypertensive (44.3% and 33.3%) than in normotensive patients (28.8%), but this was not statistically significant ($p = 0.146$). Although frequency of intraoperative hypotension was higher in patients who received inhalation anesthesia than in those given a balanced anesthesia or a combination, the difference was not significant ($p = 0.099$). The occurrence of intraoperative hypotension was significantly higher among patients who received high doses of thiopental compared with those who were given low doses or received no thiopental. Sustained intraoperative hypertension was documented in only six cases.

No patient had a myocardial infarction and there were no deaths. Forty-seven percent of patients experienced at least one postoperative complicating event of hypotension, hypertension, transient neurologic deficit, or permanent neurologic deficit (Table 2). Neurologic complications (transient or permanent) occurred in 20% of the patients with postoperative hypertension, in 6% of those with normal blood pres-

TABLE 1

Influence of Hypertension, Heart Disease, and Anesthesia on Occurrence of Intraoperative Hypotension

	No. of patients	Intraoperative hypotension*
		%
Preoperative factors		
Hypertension		
None	66	28.8
Controlled	79	44.3
Uncontrolled	21	33.3
Heart disease		
Absent	72	34.7
Present	94	38.3
Operative factors		
Anesthesia		
Inhalation	90	43.4
Balanced	56	32.1
Combination	20	20.0
Thiopental dose		
High	46	63.0†
Low	112	27.7
None	8	12.5

* Values denote relative frequency within each category.
† Significantly different from other percentages, $p < 0.01$.

TABLE 2
Postoperative Complications

Complication	No. of patients	Incidence
		%
Hypertension	50	29.5
Hypotension	22	13.3
Transient neurologic deficit	8	4.8
Permanent neurologic deficit	8	4.8
Myocardial infarction	0	0.0
Mortality	0	0.0

sure and in none of the patients who had a hypotensive episode.

The relationship of the preoperative and operative factors to postoperative hypertension, hypotension, and neurologic complications is shown in Tables 3 and 4. The incidence of postoperative hypertension was significantly greater in patients who had preoperative hypertension than in those who did not. It occurred more frequently in those whose hypertension was poorly controlled before surgery than in those in whom preoperative hypertension was well controlled. Although hypotension was observed more frequently in both groups of hypertensive patients than in those with normal preoperative blood pressure, the difference was not statistically significant. Postoperative transient neurologic deficits occurred significantly more often in patients with poorly controlled preoperative blood pressure.

The presence of other peripheral vascular disease was associated with a greater incidence of postoperative hypertension. Permanent neurologic deficit was observed more often in patients with bilateral carotid artery disease than in those with unilateral disease.

The incidence of postoperative hypertension was greater in patients who received inhalation anesthesia or a combination than in those in whom a balanced technique was used. The rate of occurrence of postoperative hypotension and neurologic deficit was not related to the anesthetic agent.

The occurrence of postoperative complications was not influenced by: (a) the coexistence of diabetes mellitus and heart disease, (b) the presenting neurologic manifestation, (c) the percentage of carotid occlusion and the presence or absence of ulcer, (d) the use of inlying shunt, (e) the use of direct intra-arterial blood pressure monitoring, or (f) the duration of anesthesia and operation.

Discussion

Although the patients in this study had a variety of coexisting medical problems, only hypertension—

TABLE 3

Influence of Preoperative Factors on Postoperative Events*

Preoperative study factors	No. of patients	Postoperative blood pressure (in patients)			Neurologic complications		
		Normal	Hypotension	Hypertension	None	PND	TND
		%			%		
Medical history							
Hypertension							
None (normotensive)	66	74.2	9.1	16.7	95.5	3.0	1.5
Controlled	79	48.1	16.5	35.4†	92.4	5.1	2.5
Uncontrolled	21	33.3	14.3	52.4‡	66.7	9.5	23.8§
Heart disease							
Absent	72	63.9	9.7	26.4	93.1	4.2	2.8
Present	94	51.1	16.0	32.9	88.3	5.3	6.4
Peripheral vascular disease							
Absent	119	62.2	12.6	25.2 ‖	91.6	5.0	3.4
Present	47	42.6	14.8	42.6	87.2	8.5	4.3
Diabetes							
Absent	123	57.7	10.6	31.7	89.4	5.7	4.9
Present	43	53.5	20.9	25.6	93.0	2.3	4.7
Presenting neurologic symptoms							
Asymptomatic bruit	13	53.8	0.0	46.2	84.6	15.4	0
Stroke	46	47.9	13.1	39.1	91.3	2.2	6.5
Transient ischemic attack	94	60.6	14.9	24.5	91.4	4.3	4.3
Other	13	61.5	15.4	23.1	84.6	7.7	7.7
Extent of carotid artery disease							
Side							
Ipsilateral	84	60.7	11.9	27.4	92.9	1.2 #	5.9
Bilateral	80	52.5	15.0	32.5	87.4	8.8	3.8
Occlusion							
<50%	40	67.5	12.5	20.0	90.0	5.0	5.0
≥50%	124	53.2	13.7	33.1	90.4	4.8	4.8
Ulcer							
Absent	92	50.0	17.4 ¶	32.6	91.4	4.3	4.3
Present	72	65.3	8.3	26.4	88.8	5.6	5.6

* Abbreviations used are: PND, permanent neurologic deficit; TND, transient neurologic deficit, PHT, postoperative hypertension
† Occurrence of PHT significantly different from patients with normotension ($p < 0.05$).
‡ Occurrence of PHT significantly different from patients with normotension ($p < 0.01$).
§ Occurrence of TND significantly different from patients with normotension and controlled hypertension ($p < 0.001$).
‖ Occurrence of PHT significantly different ($p < 0.05$).
¶ Occurrence of postoperative hypotension significantly different ($p = 0.05$).
# Occurrence of PND significantly different ($p < 0.05$).

particularly if poorly controlled—influenced eventual outcome. The increased incidence of postoperative hypertension among the patients with peripheral vascular disease might be related to the fact that 66% of these cases were also known hypertensives. Hypertension, even isolated systolic hypertension (15), has been identified as the principal risk factor for stroke. Antihypertensive therapy has been shown to prevent or delay initial or recurrent stroke (11, 12) and to reduce the incidence of many of the complications of hypertension (16). Thus, it might be expected that patients with hypertension would have a higher rate of postoperative complications following carotid endarterectomy and that control of the blood pressure might decrease the incidence to that approaching the

complication rate for normotensives. The present study suggests that although hypertensive patients have a greater incidence of postoperative hypertension than do those who are normotensive, effective preoperative blood pressure control may reduce the incidence of this complication and of postoperative neurologic deficit.

The risks of operation and anesthesia in hypertensive patients have been examined by others (1, 2, 17). Goldman and Caldera (1) prospectively studied 676 major noncardiac, non-neurologic operations in 196 patients more than 40 years of age and found that neither the preoperative systolic nor diastolic blood pressure values correlated with perioperative blood pressure lability, the development of cardiac arrhyth-

TABLE 4

Influence of Operative Factors on Postoperative Events*

Operative study factors	No. of patients	Postoperative blood pressure			Neurologic complications		
		Normal	Hypotension	Hypertension	None	PND	TND
		% of patients			%		
Anesthesia							
Inhalation	90	48.9	13.3	37.8	91.2	4.4	4.4
Balanced	56	71.4	14.3	14.3†	89.3	5.4	5.4
Combination	20	50.0	10.0	40.0	90.0	5.0	5.0
Thiopental dose							
High	46	47.8	13.0	39.1	91.3	2.2	6.5
Low	112	58.9	13.4	27.7	89.3	6.2	4.5
None	8	75.0	12.5	12.5	100.0	0.0	0.0
Intra-arterial catheter							
No	27	63.0	7.4	29.6	92.6	7.4	0.0
Yes	129	52.7	15.5	31.8	89.1	4.7	6.2
Shunt							
No	34	61.7	11.8	26.5	85.3	5.9	8.8
Yes	122	52.4	14.8	32.8	90.9	4.9	4.1

* Abbreviations used are: PND, permanent neurologic deficit; TND, transient neurologic deficit; PHT, postoperative hypertension.
† Occurrence of PHT significantly different from inhalation and combination anesthesia group ($p < 0.05$).

mias, myocardial ischemia or failure, or the incidence of postoperative renal failure. Prys-Roberts et al (2) found that patients with untreated or inadequately treated hypertension were at greater risk for the development of intraoperative hypotension and myocardial ischemia. Prys-Roberts (17) has explained the apparent differences in these findings by the fact that most of the hypertensive patients in Goldman and Caldera's study were in the mild-to-moderate range (less than 110 torr diastolic), whereas several of those studied by Prys-Roberts et al (2) had severe hypertension. Our study is in agreement with these findings, as the highest rate of complications occurred in the patients whose hypertension was poorly controlled. However, we used a lower diastolic blood pressure than 110 torr (i.e., 95 torr) as our criterion for control and found a difference in complications in patients whose blood pressure was above or below this level. In addition, we found that hypertensive patients whose pressures were controlled before surgery had a lower incidence of postoperative hypertension than did patients with poorly controlled blood pressures. Conversely, Goldman and Caldera (1) and Prys-Roberts et al (2) found that postoperative hypertension was more common in patients with histories of severe hypertension regardless of whether their pressures were well controlled before anesthesia. Others (8) have reported an increased incidence of postoperative hypertension in hypertensive patients following carotid endarterectomy, but have not evaluated the influence of treatment on this incidence. Although Bove et al (7) demonstrated a significant correlation

between hypertension and postoperative hypotension, our study and that of Tarlov et al (5) did not.

The association of postoperative hypertension with neurologic deficit, which has been reported previously (7, 8), was also demonstrated in this study. Conversely no correlation between postoperative hypotension and neurologic deficit was seen. Both complications were treated promptly and thus persistence of one blood pressure abnormality or the other could not account for the difference.

Sundt and colleagues (18) found severe hypertension (blood pressure 180/110 torr) to be an important risk factor in patients undergoing carotid endarterectomy. Our data suggest that blood pressure should be under even better control than this before surgery, as patients with pressures higher than 170/95 torr had an increased incidence of neurologic deficit, whereas those with blood pressures below this level did not have an incidence of neurologic deficits significantly different from that observed in normotensive patients.

Our findings suggest that a patient scheduled for elective carotid endarterectomy whose hypertension is poorly controlled might benefit from better preoperative blood pressure control. The findings do not indicate, however, the optimum length of time before surgery during which this control should be established and maintained. The anesthesiologist presented with such a patient, who is scheduled for endarterectomy the following day, possesses no useful guidelines as to how to proceed. It would not be in the patient's best interest to decrease pressure acutely and then proceed with surgery. Individuals with hyperten-

sion have a cerebral autoregulatory curve that is shifted to the right, i.e., both the upper and lower limits of mean arterial pressure between which cerebral blood flow remains relatively constant are higher than they are in normotensive individuals. This tends to return toward normal with effective antihypertensive therapy, but the change may require several months (19). Meyer and colleagues (20) demonstrated that 2 weeks of antihypertensive therapy resulted in a slight increase (8.2 ml/100 g of brain/min) in cerebral blood flow in nine of 13 patients with poorly controlled hypertension and cerebrovascular symptoms. Cerebral blood flow decreased slightly (3.8 ml/ 100 g of brain/min) in four patients whose mean arterial pressure was reduced to a greater extent (average = 25 mm Hg).

A gradual reduction of blood pressure during a period of 2 to 4 weeks before surgery may be the best approach to the treatment of these patients. The data presented here suggest that pressure need not be greatly reduced as those patients whose blood pressures did not exceed 170/90 torr with antihypertensive therapy had an overall neurologic outcome that did not differ significantly from that of normotensive patients. If surgery cannot be delayed, it is probably best not to decrease blood pressure acutely, but rather to maintain it in the patient's customary range during the perioperative period.

Anesthesia for carotid endarterectomy has been successfully managed with a variety of intravenous, inhalation, and regional techniques; each has advantages and disadvantages. Aside from a lower incidence of postoperative hypertension in those who received balanced anesthesia, our study did not demonstrate any association between postoperative complications and the anesthetic used. This was true when large doses (15 mg/kg) of thiopental were given before carotid artery clamping, as well as when the drug was used in smaller doses for induction of anesthesia. There was, however, an increase in the number of patients requiring intraoperative vasopressor therapy in patients given high doses of thiopental. It should be pointed out that this was not a controlled trial of the efficacy of barbiturate administration in preventing neurologic complications following carotid endarterectomy and no conclusions concerning its value in this situation should be drawn from this study.

Although no relationship was found between the use of direct intra-arterial monitoring of blood pressure and the incidence of complications, we feel that such monitoring is extremely valuable as control of

blood pressure and arterial blood gas tensions is an important part of the perioperative management of patients undergoing carotid endarterectomy (21).

No myocardial infarctions and no deaths occurred in this series. A strong correlation between the incidence of myocardial infarction and preexisting heart disease, particularly coronary artery disease, has been documented in patients undergoing carotid artery surgery (18, 22–24). Rubio and Guinn (22) reported perioperative fatal myocardial infarctions in 16% of their patients with diagnosed coronary artery disease, whereas Ennix et al (23) showed that 14% of patients with symptomatic coronary artery disease at the time of carotid surgery had a fatal myocardial infarction.

In our series, heart disease was present in 57% of patients and although none of them had unstable angina at the time of surgery, there was verifiable evidence of coronary artery disease in 55% of this group. The fact that no documented case of perioperative myocardial infarction was observed might be related to the routine maintenance of blood pressure within 10% of the upper range of the pressure considered normal for each individual. Prompt pharmacologic intervention was the rule for hypertensive as well as hypotensive episodes. Phenylephrine (0.002%) was our agent of choice for the treatment of hypotension. The reflex bradycardia produced by this predominantly alpha-adrenergic agonist may help in maintaining myocardial oxygen demand within acceptable limits. Agents possessing both alpha- and beta-adrenergic agonistic effects could more easily produce an imbalance of myocardial oxygen demand and supply in patients who are at risk because of coronary artery disease. The increased incidence of perioperative myocardial infarction reported in patients with heart disease in whom metaraminol was used to maintain blood pressure during carotid artery clamping (24) might reflect this phenomenon. Intraoperative vasopressors were administered to 35% of our patients with heart disease and no myocardial infarctions occurred.

In conclusion, perioperative factors that unfavorably affected neurologic outcome following carotid endarterectomy included poor preoperative blood pressure control, the presence of bilateral carotid artery disease, and the development of postoperative hypertension. The incidence of this latter complication was also shown to be related to the degree of preoperative blood pressure control. These findings suggest that among the various factors under control of the anesthesiologist, strict regulation of blood pres-

sure, not only during surgery but also before and after surgery, is extremely important in the management of patients undergoing carotid endarterectomy.

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Maternal, Fetal, and Neonatal Responses after Epidural Anesthesia with Bupivacaine, 2-Chloroprocaine, or Lidocaine

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The effects of epidural analgesia on fetal heart rate, fetal heart rate variability, uterine activity, maternal blood pressure, newborn Apgar scores, neonatal acid base status, and the early neonatal neurobehavioral status were studied in 150 parturients during labor and delivery. Group I (n = 50) received 0.5% bupivacaine, group II (n = 50) received 2% 2-chloroprocaine, and group III (n = 50) received 1.5% lidocaine. None of the three local anesthetics used had any significant effect on either base line fetal heart rate, beat-to-beat variability, or uterine activity. In cases in which monitoring of fetal heart rate was both technically satisfactory and continuous, late deceleration patterns were seen in 8 of 42, 0 of 34, and 3 of 47 of the fetuses in groups I, II, and III, respectively. The difference in incidence of late deceleration patterns between groups I and II was statistically significant ($p < 0.025$). Early neonatal neurobehavioral status did not differ among the three groups of neonates nor did any of the neonates in the three groups score lower than a control group of 20 neonates whose mothers did not receive any analgesia or medications for labor or delivery. It is concluded that epidural anesthesia as administered in this study has no significant effect on the base line fetal heart rate, uterine activity, or neurobehavioral status of the neonate, and that bupivacaine is associated with a higher incidence of what appears to be transient abnormalities of fetal heart rate.

EPIDURAL analgesia for labor and delivery has gained widespread use because of its effectiveness and, when properly conducted, its safety. 2-Chloroprocaine (1, 2), lidocaine (3–9), and bupivacaine (10–18) are currently widely used, but no detailed comparative study of the effects of these agents on fetal heart rate, fetal heart rate variability, or uterine activity has been reported. The present study

was undertaken to determine the effect of these local anesthetics on the mother, fetus, and neonatal outcome, as well as to measure the plasma levels of these agents.

Methods and Materials

One hundred fifty laboring parturients at term with no obstetric or medical complications who elected to have epidural analgesia for labor and delivery were studied. The study was approved by the Committee on Human Experimentation and informed consent was obtained from each patient. The patients received no intravenous medications within 30 minutes and no intramuscular medications within 1 hour before the onset of the study period. All patients had ruptured membranes. Utilizing a Corometrics 112 fetal monitor, uterine activity was monitored with a transcervical intrauterine catheter and fetal heart rate (FHR) was directly monitored with a scalp electrode. Fetal heart rate variability was also recorded using the template of Hon (19). Maternal heart rates and blood pressures were monitored throughout the study period using precordial stethoscopes and sphygmomanometers.

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Before induction of epidural anesthesia, all fetuses had normal FHR patterns.

With patients in the left lateral decubitus position, epidural catheters were placed at L3–4 interspace and advanced 2 cm cephalad. Patients were then placed in the supine position with left uterine displacement. All patients were given 500 ml of 5% dextrose in lactated Ringer's solution and, after measurement of FHR, fetal heart rate variability, uterine activity, and maternal blood pressure for 30 minutes, patients were given one of three local anesthetics in a random manner. Group I (n = 50) received bupivacaine 0.5%; group II (n = 50) received 2% 2-chloroprocaine; group III (n = 50) received 1.5% lidocaine. Epinephrine-containing solutions were not used. If 5 minutes after a test dose of 2 ml of local anesthetic was injected there was no evidence of subarachnoid injection, the remainder of the local anesthetic was administered. The dose was chosen to provide analgesia to a level of T-10, taking into consideration the height of the patient. Local anesthetics were reinjected as clinically indicated and observations continued until delivery of the infant in 42, 34, and 47 patients for groups I, II, and III, respectively. The remainder of the patients were only observed up to 60 minutes following the injection of the local anesthetics into the epidural space and at time of delivery.

Duration of analgesia was defined as the time from onset of pain relief until the time of onset of discomfort. The overall quality of the analgesia was evaluated using our routine scale ranging from 0 for no pain relief to 4+ representing excellent analgesia. Maternal hypotension was considered to be present whenever systolic blood pressure decreased more than 30 torr or to less than 100 torr. Hypotension was corrected by increasing the rate of intravenous fluid infusion and by administration of intravenous ephedrine.

Maternal venous blood samples for measurement of local anesthetic concentrations were obtained from an indwelling venous catheter 5 minutes after injection of the local anesthetic agent into the epidural space and at the time of delivery. Also, blood was collected from a doubly clamped section of umbilical cord for measurement of local anesthetic levels and acid base status. All samples were immediately put into heparinized tubes containing 0.3 ml of echothiophate iodide, a cholinesterase inhibitor (Ayerst Laboratories, Los Angeles, CA). The plasma was removed following centrifugation and frozen until assayed for drug levels using modification of the gas chromatographic technique of Mather and Tucker (20).

Neonates were evaluated by Apgar scores at 1 and

5 minutes, cord acid base status at time of delivery, and early neonatal neurobehavioral scale (ENNS) at 2 and 24 hours of age, according to a previously described protocol (21). Apgar scores were assigned by pediatricians who were blind to the local anesthetic administered. The neurobehavioral examination was performed by a trained anesthesia research fellow. Variables in the neurobehavioral examination were scored on a scale from 0 to 3, with 0 and 1 being absent or weak responses (low scores) and 2 and 3 being moderate or brisk responses (high scores). Results of the ENNS were compared with ENNS results obtained in a group of 20 control babies whose mothers did not receive any analgesics or medications for labor or delivery. Persons who administered the anesthetics and those who evaluated the mother, fetus, and neonate, including the control group, were completely blind to the local anesthetic administered.

Data were analyzed for statistical significance using analyses of variance, Student's t-test, and chi-square when appropriate. A p value of less than 0.05 was considered statistically significant.

Results

Data on maternal age, weight, height, parity, infant gestational age, and weight are summarized in Table 1. With the exception of statistically significant differences in maternal and infant weights, there were no significant differences among the three groups with regard to patient characteristics.

Effects on Mother

Sixteen patients developed hypotension (five in group I, eight in group II, and three in group III). The incidence was not statistically different among the three groups and in no case did it last longer than 2

TABLE 1

Patient Data*

	Bupivacaine (n = 50)	2-Chloropro-caine (n = 50)	Lidocaine (n = 50)
Maternal age (yr)	23.3 ± 4.8	22.6 ± 4.9	21.9 ± 4.3
Maternal weight (kg)	66.9 ± 10.7	72 ± 11†	67.6 ± 10.7
Maternal height (cm)	155 ± 10	157.5 ± 5	155 ± 8
Parity	2.0 ± 1.6	1.7 ± 1.3	1.9 ± 1.3
Gestational age (wk)	39.9 ± 2.9	40 ± 1.9	39.7 ± 2.5
Infant weight (gm)	3351 ± 528	3659 ± 505‡	3390 ± 441

* Values are means ± SD.

† p < 0.01 compared to bupivacaine and lidocaine by Student's t-test.

‡ p < 0.001 compared to bupivacaine and lidocaine by Student's t-test.

minutes. Ephedrine was given to nine patients. Mean systolic and diastolic blood pressures showed a statistically significant decrease 20 to 40 minutes after administration of all three local anesthetics ($p < 0.05$) (Fig 1). The quality of the analgesia was either 3+ or 4+ in all patients. Duration of analgesia in minutes (mean ± SD) was 115 ± 36 for bupivacaine, 46 ± 14 for chloroprocaine, and 52 ± 18 for lidocaine.

Effects on Fetus

There were no significant changes in the mean base line FHR (Fig 2) or fetal heart rate variability (Fig 3) with any of the three local anesthetics. Following injection of the local anesthetic into the epidural space, changes were observed in periodic FHR patterns as defined by Kubli et al (22), by which we mean late and variable decelerations. Ten of the 42 patients receiving bupivacaine, two of 34 patients receiving 2-chloroprocaine, and eight of 47 patients receiving lidocaine showed these patterns. Following bupivacaine, two fetuses had prolonged deceleration in the base line heart rate lasting 7 and 10 minutes, respectively. Both were associated with increased irregularity of the base line. Six fetuses in the same group had moderate to severe late deceleration 3 to 17 minutes following injection of bupivacaine and two fetuses had from two to four mild/or moderate variable decelerations observed 8 to 17 minutes after
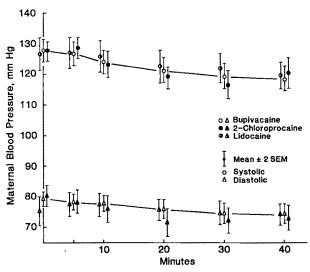
FIG 1. Effects of epidural anesthesia with bupivacaine, 2-chloroprocaine, or lidocaine on maternal systolic and diastolic blood pressures after first injection of local anesthetic into epidural space (mean ± 2 SEM). There were 50 patients in each group. There were statistically significant decreases in both systolic and diastolic blood pressures 20 to 40 minutes after injection of all three local anesthetics ($p < 0.05$) as determined by Student's t-test.
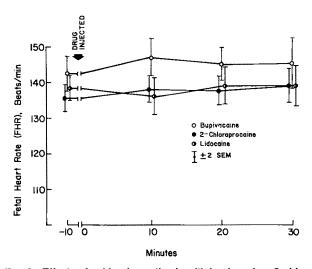
FIG 2. Effects of epidural anesthesia with bupivacaine, 2-chloroprocaine, or lidocaine on fetal heart rate (mean ± 2 SEM). No changes were statistically significant by Student's t-test.
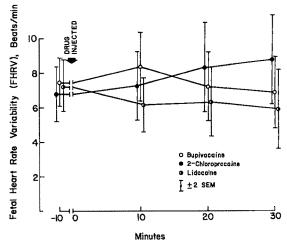
FIG 3. Effects of epidural anesthesia with bupivacaine, 2-chloroprocaine, or lidocaine on fetal heart rate variability (mean ± 2 SEM). No changes were statistically significant by Student's t-test.

injection. After receiving 2-chloroprocaine, two fetuses had mild variable deceleration within 18 minutes of the injection. After lidocaine the changes were observed 7 to 18 minutes following injection, five fetuses having mild and/or moderate variable deceleration, whereas three fetuses had moderate late decelerations. To summarize, late deceleration patterns occurred in eight fetuses following administration of bupivacaine, in three fetuses after lidocaine, and in none following 2-chloroprocaine. The difference in incidence between groups I and II was statistically significant ($p < 0.025$). In all cases adverse changes in FHR lasted for two to seven contractions with the exception of one fetus in the bupivacaine group in

which variable deceleration persisted until delivery. These abnormal patterns were not associated with maternal hypotension except for one case in which bupivacaine was given, neither were they associated with increased uterine activity or abnormally high drug levels in the mother or the neonate. All fetuses who developed these patterns had good outcome as ascertained by the Apgar scores, cord acid base status, and ENNS.

Effects on Uterine Activity

Uterine activity, as measured by the number of contractions per 10 minutes (Fig 4), was not significantly affected by any of the three local anesthetics.

Maternal and Fetal Plasma Anesthetic Levels

Plasma levels of local anesthetics are presented in Tables 2 and 3. The fetal-to-maternal ratios of plasma concentrations of local anesthetics were 0.30 and 0.70 for bupivacaine and lidocaine, respectively. 2-Chlo-

roprocaine was detected in eight of 50 maternal samples 5 minutes after injection of local anesthetics, in two of 30 maternal samples at time of delivery, in three of 25 umbilical venous samples, and in two of 22 umbilical arterial samples. The fetal-to-maternal ratio of plasma levels of 2-chloroprocaine was 0.83 in the samples with detectable levels.

Effects on Newborn

There was no significant difference between the incidence of low 1- and 5-minute Apgar scores among the three groups (Table 4).

Cord Acid-Base Status

Neonatal acid-base status remained within normal limits in the three groups (Table 5).

Early Neonatal Neurobehavioral Scores

The results of the neurobehavioral scores of the three groups of neonates whose mothers received epidural analgesia and the neonates of the control group whose mothers did not receive any anesthesia are presented in Tables 6 and 7. The latter group was comparable to the other three groups in regard to maternal age, parity, height, weight, and infants' gestational age, weight, and Apgar scores. ENNS was determined only in babies whose mothers had normal

FIG 4. Effects of epidural anesthesia with bupivacaine, 2-chloroprocaine, or lidocaine on uterine activity (mean ± 2 SEM). No changes were statistically significant by Student's t-test.

TABLE 2

Plasma Concentrations of Bupivacaine and Lidocaine*

	Bupivacaine	Lidocaine
	μg/ml	
Maternal vein		
5 min after injection	0.30 ± 0.02 (n = 50)	0.74 ± 0.05 (n = 50)
At time of delivery	0.30 ± 0.05 (n = 29)	1.22 ± 0.11 (n = 41)
Umbilical vein	0.10 ± 0.02 (n = 28)	0.80 ± 0.07 (n = 37)
Umbilical artery	0.13 ± 0.05 (n = 21)	0.70 ± 0.07 (n = 24)
Umbilical vein/ maternal vein	0.30 ± 0.02	0.70 ± 0.06

* Values are means ± SE.

TABLE 3

Mean Maternal and Fetal 2-Chloroprocaine Plasma Concentrations

	Total no. of samples	No. of samples with detectable levels	2-Chloroprocaine levels*
			ng/ml
Maternal vein			
5 min after injection	50	8	10.0 ± 1.6
At delivery	30	2	12.05 ± 1.7
Umbilical vein	25	3	10.0 ± 1.8
Umbilical artery	22	2	9.1 ± 3.8
Umbilical vein/ maternal vein			0.83

* Values are means ± SE.

TABLE 4

Neonates with Low Apgar Scores*

Apgar Score	Group I bupivacaine (n = 50)	Group II 2-chloroprocaine (n = 50)	Group III lidocaine (n = 50)
1 min	7	9	6
5 min	1	0	0

* No significant difference between groups by chi-square.

TABLE 5

Acid-Base and Blood Gas Data*

	Bupivacaine	2-Chloropro-caine	Lidocaine
Umbilical vein			
No.	32	34	38
pH	7.34 ± 0.01	7.32 ± 0.01	7.33 ± 0.01
P_{O_2} (torr)	30.9 ± 1.4	29.4 ± 1.2	29.0 ± 0.8
P_{CO_2} (torr)	35.7 ± 1.1	35.9 ± 1.0	36.5 ± 1.5
Base excess (meq/L)	6.5 ± 0.5	6.6 ± 0.5	6.2 ± 0.4
Umbilical artery			
No.	31	32	39
pH	7.26 ± 0.01	7.23 ± 0.02	7.25 ± 0.01
P_{O_2} (torr)	19.8 ± 0.9	19.0 ± 0.9	20.3 ± 0.8
P_{CO_2} (torr)	42.1 ± 1.8	47.1 ± 1.8	43.6 ± 1.8
Base excess (meq/L)	7.0 ± 0.8	7.0 ± 0.8	7.9 ± 0.6

* Values are means ± SE. No significant difference between groups by Student's t-test.

spontaneous or low forcep deliveries regardless of whether the mothers had epidural anesthesia or no anesthesia. There were no significant differences in ENNS among the three local anesthetic groups, nor did any of these groups score lower than the control group in any of the variables of the test.

Discussion

One of the important findings of the present study is the lack of adverse neurobehavioral effects of lidocaine on the newborn. Our findings differ from those reported by Scanlon et al (21), who found that infants whose mothers received epidural anesthesia with either lidocaine or mepivacaine scored less well in tests designed to assess muscle strength and tone than did infants delivered without epidural anesthesia. The relatively small dose of lidocaine used in our study (240 ± 17 mg) might have been a factor accounting for the observed difference in the results of the two studies. We found that giving a small volume and a low concentration of the local anesthetics and giving them only when needed, provided adequate analgesia without impairing the ability of the parturients to push during the second stage.

Maternal and fetal plasma levels of local anesthetics found in the present study and in Scanlon's study are shown in Table 8. These results show no significant differences for the local anesthetic plasma levels in the two studies.

Another important finding of the present study was the high incidence of late deceleration fetal heart patterns associated with bupivacaine epidural anes-

TABLE 6

Percentage of Neonates (at Ages 2 and 24 Hours) with High Neurobehavioral Scores after Lumbar Epidural Anesthesia with Bupivacaine, 2-Chloroprocaine, or Lidocaine*

	Bupiva-caine (n = 20)	2-Chloropro-caine (n = 15)	Lidocaine (n = 21)	Control (n = 20)
	%			
Alertness				
2	75	53	67	70
24	100	73	90	95
General assessment				
2	90	87	86	100
24	100	100	95	85
State				
2	65§	53‡	34	10
24	78†	87§	71‡	30
Pull to sit				
2	60	60	62	90
24	83	80	81	95
Arm recoil				
2	70	73	76	55
24	78	73	76	85
Truncal tone				
2	65	60	67	60
24	83	80	86	85
Body tone				
2	80	73	76	85
24	94	87	86	100
Rooting				
2	15	40	38	25
24	33	53	57	35
Sucking				
2	65	87†	81†	35
24	89	89	76	70
Moro				
2	75	60	86	55
24	89	67	71	70
Placing				
2	75	60	71	80
24	78	80	86	85

* Statistical significance between control and bupivacaine is indicated after bupivacaine, between control and 2-chloroprocaine after 2-chloroprocaine, and between control and lidocaine after lidocaine.
† $p < 0.01$.
‡ $p < 0.025$.
§ $p < 0.005$ by chi-square.

thesia. Changes in FHR and neonatal acid-base balance after epidural anesthesia have been described by other investigators (24–28), but the etiology of these changes remains undefined. Changes in FHR could be due to inadequate uterine blood flow as these patterns disappeared after repositioning the patient and administration of oxygen and intravenous fluids. Direct toxic effects of the local anesthetics, including myocardial depression, could also be a contributing cause. Bupivacaine has achieved popularity in obstetrics in part because of its long duration of action and high degree of protein binding which has been said to limit its placental transfer. However, recent evi-

dence (H. O. Morishima and M. Finster, personal communication, 1975) comparing lidocaine, bupivacaine, and etidocaine in guinea pigs suggests that the lower fetal blood levels may be due to higher fetal tissue uptake rather than a reduced transfer across the placenta. In their study, uptake of bupivacaine into fetal myocardium, brain, and liver was substantially greater than that of lidocaine. This was due to the fact that bupivacaine is 10 times more soluble in lipids than is lidocaine. Higher protein binding of bupivacaine (protein binding of bupivacaine in guinea pigs is similar to that in humans) failed to limit its placental transfer and the relatively low fetal blood level of this drug can be explained on the basis of greater tissue uptake. However, it is unlikely that the deceleration patterns observed in the present study were due to direct toxic effect as they were so brief in duration. Although uterine hypertonus has been suggested as a cause of bradycardia occurring during paracervical

block, in our series we found no increase in uterine activity during epidural anesthesia. Another possible explanation for changes in FHR is uterine artery vasoconstriction which has been shown to reduce significantly uterine blood flow out of proportion to any increase in uterine activity in both human subjects and experimental animals (29–31). This may occur without any appreciable decrease in systemic blood pressure. An alternate hypothesis suggests that umbilical arterial spasm may result in a reflexly induced variable deceleration. Morishima et al (32), have demonstrated reduced umbilical blood flow in acidotic fetal sheep after intravenous local anesthetics were given to the mother, possibly evidence of umbilical arterial spasm. Unfortunately, in our study we did not monitor fetal electrocardiograms, which would have been helpful to define whether the mechanism is due to hypoxia or due to a direct effect of local anesthetics on the fetal myocardium. Freeman and associates (33) evaluated fetal heart rate and fetal electrocardiogram changes following paracervical block. The fetal electrocardiogram changes during the bradycardia patterns after paracervical block more closely resembled changes consistent with hypoxia than with direct toxic effect on the fetal myocardium.

In the present study, all the above etiologic factors could be incriminated in the changes in fetal heart rates that we observed. Whatever the mechanism of these patterns might have been, neonatal outcome was invariably good. However, in this study we only studied parturients with no medical or obstetric complications. In cases of compromised or borderline uteroplacental function, the lowest possible effective dosage of local anesthetics should be utilized for epidural anesthesia and injections should be adequately spaced to avoid excessive increases in maternal and fetal blood levels of the local anesthetics.

ACKNOWLEDGMENTS

TABLE 7

Percentage of Neonates (at Ages 2 and 24 Hours) with Response Decrements after Delivery Using Lumbar Epidural Anesthesia with Bupivacaine, 2-Chloroprocaine, or Lidocaine*

	Bupivacaine (n = 20)	2-Chloroprocaine (n = 15)	Lidocaine (n = 21)	Control (n = 20)
	%			
Pin prick decrement				
2	89	100	62	100
24	100	100	71	100
Sound decrement				
2	95	100	100	90
24	83	100	100	100
Light decrement				
2	95	100	100	90
24	94	100	100	90
Moro decrement				
2	100	100	100	100
24	100	100	100	100

* No significant difference between four groups by chi-square.

TABLE 8

Plasma Concentrations of Local Anesthetic at Time of Delivery in Present Study and in Studies of Scanlon et al*

	Bupivacaine		Lidocaine	
	Abboud et al (n = 20)	Scanlon et al (23) (n = 20)	Abboud et al (n = 21)	Scanlon et al (21) (n = 9)
	μg/ml			
Maternal vein	0.31 ± 0.07	0.41 ± 0.05	1.19 ± 0.10	—
Umbilical vein	0.11 ± 0.03	0.11 ± 0.02	0.68 ± 0.06	—
Umbilical artery	0.15 ± 0.09	0.10 ± 0.01	0.56 ± 0.10	0.48
Umbilical vein/maternal vein	0.31 ± 0.02	0.27 ± 0.01	0.63 ± 0.06	—

* Values are means ± SE. No significant difference between local anesthetic plasma levels in the two studies by Student's t-test.

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Cardiopulmonary Resuscitation with Interposed Abdominal Compression in Dogs

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This study was conducted to evaluate the hemodynamic effectiveness of a new modification of cardiopulmonary resuscitation (CPR), termed interposed abdominal compression-CPR (IAC-CPR). IAC-CPR utilizes all the steps of standard CPR with the addition of abdominal compressions interposed during the release phase of chest compression. Ventricular fibrillation was induced electrically in 10 anesthetized dogs, and either IAC-CPR or standard CPR was initiated while arterial and venous blood pressures and cardiac output were monitored. The two CPR methods were alternated every 3 minutes over a period of 30 minutes. The addition of interposed abdominal compressions to standard CPR improved arterial pressures and perfusion in 10 of 10 dogs. Brachial arterial blood pressure averaged 87/32 mm Hg during IAC-CPR vs 58/16 mm Hg during standard CPR. Cardiac output (±SE) averaged 24.2 ± 5.7 ml/min/kg during IAC-CPR vs 13.8 ± 2.6 ml/min/kg during standard CPR. IAC-CPR requires no extra mechanical equipment, and, if proven effective in human trials, may improve resuscitation success in the field and in the hospital.

Key Words: VENTILATION: resuscitation; HEART: resuscitation; COMPLICATIONS: cardiac arrest, resuscitation.

RECENTLY several modifications of cardiopulmonary resuscitation (CPR) that generate improved blood flow compared with standard CPR (1), have been discovered in the laboratory and tested on a limited basis in the clinic. Improvements in blood pressures and blood flows during experimental CPR have, for example, been reported with increased duration of chest compression (2, 3), with simultaneous chest compression and ventilation at high airway pressure (4–6), with negative diastolic airway pressure (7), and with abdominal binding (8). These studies leave little doubt that improved blood flow is possible during CPR, and they provide valuable insights into mechanisms that generate blood flow during CPR (9). However, because special mechanical equipment is necessary, techniques such as simultaneous chest compression and ventilation at high airway pressure or application of negative diastolic airway pressure constitute advanced life-support techniques not applicable to field resuscitation by basic rescuers or to initial attempts at resuscitation in the hospital. Manual versions of CPR with simultaneous compression and ventilation have been developed and tested by Redding et al (10) and by Gordon and co-workers (11), but were not recommended as significantly better than standard CPR.

This report describes animal studies of a new form of modified CPR which seems applicable to basic life support. It can be performed by two or three rescuers with no equipment other than their bare hands. It includes all the procedures of standard CPR and so constitutes an evolution rather than a revolution in technique. We have termed this modification interposed abdominal compression-CPR (IAC-CPR).

IAC-CPR

This technique involves standard ventilation and chest compression with the addition of abdominal compressions interposed between chest compressions. The method was discovered by one of us (S.H.R.) serendipitously during a difficult resuscitation in the animal laboratory. CPR is performed exactly as recommended in current American Heart Association standards (1), and in addition the abdo-

men is compressed alternately or reciprocally as chest compression is released. This technique of abdominal counterpulsation necessarily would require two or three rescuers, as shown in Fig 1.

Having observed significantly improved arterial blood pressure during the chance discovery of IAC-CPR as compared with standard CPR, we conducted the following research to determine whether arterial pressures and cardiac output were consistently improved by the addition of alternate abdominal compressions to the mechanics of standard CPR.

Methods

To compare blood flow generated by IAC-CPR with that generated by standard CPR, we measured cardiac output during alternate 3-minute trials of the two techniques in animals during electrically induced ventricular fibrillation, using a modified indicator dilution-modified technique adapted to the low flow conditions of CPR. We compared IAC-CPR and standard CPR in both large and small mongrel dogs, as the size of animals studied may substantially influence the outcome of CPR experiments (6).

Ten mongrel dogs were selected for the study. The five large dogs weighed 15 to 26 kg (mean 18.9 kg),
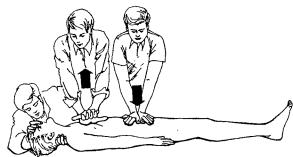
FIG 1. Artist's conception of basic rescuers performing IAC-CPR. For clarity, rescuers are shown on the same side of the victim. Top, with two rescuers, the first compresses chest and ventilates while the second compresses abdomen. Bottom, with three rescuers, ventilation, chest compression, and abdominal compression are each performed by a single individual.

had dorsal-ventral chest diameters ranging from 21 to 25 cm (mean 23 cm) at the level of the heart, and chest circumferences of 57 to 61 cm (mean 60 cm). The five small dogs weighed 9 to 13 kg (mean 11.6 kg), had dorsal-ventral chest diameters ranging from 16 to 21 cm (mean 19 cm) at the level of the heart, and chest circumferences of 45 to 53 cm (mean 49 cm).

The dogs had free access to food and water before anesthesia. Each animal was anesthetized with pentobarbital sodium (30 mg/kg IV). The trachea was intubated with the largest possible cuffed tracheal tube. The following catheters were inserted: (a) a pigtail catheter was advanced into the left ventricle via a femoral artery for injection of indicator to measure cardiac output, (b) a 40-cm long, 0.1-cm i.d. catheter was advanced to the thoracic aorta and attached to a motor-driven syringe for withdrawal of blood during inscription of dilution curves, (c) a catheter to monitor arterial pressure was advanced 5 to 10 cm into the right brachial artery, (d) a catheter to monitor central venous pressure was advanced via the left femoral vein into the right atrium. The catheters used for arterial and venous pressure monitoring were connected to matched Statham pressure transducers. Heparin (1 mg/kg IV) was given to retard clot formation in the catheters, to permit reinfusion of blood withdrawn during inscription of dilution curves, and to diminish intravascular coagulation during CPR.

The animal was placed in dorsal recumbency on a V-shaped board with the limbs securely tied to the board to prevent lateral motion of the chest during CPR. A Thumper mechanical resuscitator (Michigan Instruments, Inc., Grand Rapids, MI) was used for chest compression and ventilation. Subcutaneous electrodes for recording the electrocardiogram (lead II) were secured in place, and wire mesh electrodes for sternal-to-back defibrillation were applied to the shaved skin of these regions with electrolytic gel. The V-shaped, 20x20-cm back electrode for defibrillation conformed to the animal board, and the wire mesh of the sternal electrode was molded to the chest compression pad of the Thumper. The chest compression pad was rectangular in shape and 6x10 cm in dimension.

The pad used for abdominal compression was a standard 12-cm width blood pressure cuff folded to rectangular dimensions of 12x15 cm and inflated with air to a thickness of 3 cm. The bladder of the cuff was attached via the filling hose to an aneroid manometer and to a linear core pressure transducer in order to monitor pressure applied to the abdomen. IAC-CPR

was performed by manual compression of the mid-abdomen with this inflated pad in a way that generated pressure pulses of 120 to 150 mm Hg. The duty cycle of abdominal compression was complementary to that of chest compression i.e., 50% of cycle time (0.5-second abdominal compression duration). The position of the hands for abdominal compression was similar to that used in basic CPR for manual chest compression except that the fingers were spread to provide a larger surface area of compression approximately equal to that of the flattened blood pressure cuff.

Physiologic Monitoring

A five-channel graphic record was inscribed using a Physiograph direct-inking recorder (Narco Bio-Systems, Houston, TX). Channels 1, 2, 3, and 4 displayed the electrocardiogram, arterial blood pressure, venous blood pressure, and abdominal compression pressure, respectively. Pressure channels were calibrated and their linearity was confirmed using a mercury manometer.

Channel 5 of the graphic record displayed indicator dilution curves for measurement of cardiac output by the saline-conductivity method (12), specially modified for the low flow conditions of CPR (13). This method uses 5% NaCl solution as the indicator and a calibrated, flow-through conductivity cell as the detector. Its accuracy has been confirmed by comparison with the direct Fick method under conditions of CPR (14). Aliquots (2 ml) of 5% saline indicator were injected forcibly into the left ventricle and blood samples were withdrawn through the detector via the catheter placed in the thoracic aorta. This injection-sampling configuration permits mixing of indicator in blood during CPR adequate for accurate measurements of cardiac output (13).

Experimental CPR

After control measurements of blood pressure and cardiac output were obtained, a single episode of ventricular fibrillation was produced by 60 Hz electrical stimulation of the left ventricular endocardium. A fine, 0.1-mm, stainless steel wire threaded through the lumen of the left ventricular catheter carried electric current to the heart for this purpose. Immediately after electrocardiographic confirmation of fibrillation, ventilation and chest compression were initiated using the Thumper driven with 100% oxygen at 60 psi. This device provided standard CPR continuously throughout the experiment.

The technique of abdominal compression was added to the CPR provided by the Thumper during alternate 3-minute intervals. Five 3-minute trials of IAC-CPR and five 3-minute trials of standard CPR were evaluated alternately in the same animal during one continuous episode of ventricular fibrillation. In half of the dogs IAC-CPR was started first and in half of the dogs standard CPR was started first. After a 30-second recording of pulsatile blood pressures for a given mode of CPR, dilution curves were obtained. Then the mode of CPR was changed and the process repeated. In this sense, each animal served as its own control.

During both standard CPR and IAC-CPR, the ventilation pressure was 20 cm H_2O, the ventilation duration was 0.5 second, and ventilations were interposed after every fifth chest compression. The chest compression force, 40 to 80 lb for small dogs and 60 to 120 lb for large dogs, was selected to produce approximately equal sternal displacement as a percentage of dorsal-ventral chest diameter (mean 25%) in the two groups of dogs. In each dog the same force of chest compressions was maintained for both standard and IAC-CPR. In both standard and IAC-CPR the compression rate was 60/min, and the duty cycle of compression was 50% of cycle time (compression duration = 0.5 second).

Postresuscitation Protocol

After the 10 consecutive trials of standard and experimental CPR, electrical shock was applied to defibrillate the ventricles. If necessary, intracardiac epinephrine was given via the left ventricular catheter to promote recovery of the circulation. After recovery of the circulation the animal was monitored for 30 minutes to determine whether any lethal complications of the experiment had occurred. Then the animal was killed by ventricular fibrillation without resuscitative measures and a thorough gross postmortem examination was performed. Special attention was given to identification of possible trauma to the abdominal viscera as a result of IAC-CPR.

Data Analysis

To compare effects of experimental CPR, mean cardiac output during the five trials of standard CPR and the five trials of IAC-CPR was calculated for each animal. Student's t-test for paired data was used to test the null hypothesis that these mean values of cardiac output per kilogram were the same during IAC-CPR and standard CPR in the population of 10

dogs. A similar analysis was performed for measurements of brachial arterial and venous blood pressures and of the arteriovenous pressure difference. If necessary, a square root transformation was performed on the data before calculation of Student's t statistics, to satisfy the assumption of approximate normality of the sampling distribution required for the t-test (15, 16).

Results

Cardiac Output

Cardiac output generated by IAC-CPR was greater than that generated by standard CPR in every animal (Fig 2). In Fig 2 each data point represents the mean of five measurements in a single dog and each symbol type represents a given animal. The paired differences in mean cardiac output for the 10 dogs are significantly different from zero ($p < 0.005$, $t = 4.79$, $df = 9$). If the mean cardiac output during standard CPR in each dog is assigned a value of 100%, the corresponding values during IAC-CPR ranged from 122% to 372%. Within a given animal the coefficient of variation (SD/mean) of the five cardiac output measure-

ments ranged from 11% to 33% (mean 21%) during standard CPR and from 4% to 34% (mean 18%) during IAC-CPR.

Blood Pressures

Maximal (systolic) and minimal (diastolic) arterial pressures were higher during IAC-CPR than during standard CPR in all 10 dogs (Figs 3 and 4). The central diastolic arteriovenous pressure gradient, which may be critical for coronary perfusion, was improved during IAC-CPR in eight of 10 dogs (Fig 5). The sets of paired differences in systolic and diastolic arterial pressure and in the arteriovenous pressure difference for the 10 dogs are each significantly greater than zero ($p < 0.01$).

Other Observations

Abdominal counterpulsation did not cause obvious regurgitation of gastric contents in any of the 10 dogs, even though the animals had not fasted before the experiment. After defibrillation, seven of the 10 dogs survived for 30 minutes. No significant gross trauma to intra-abdominal organs was seen at postmortem examination. Serosanguinous abdominal fluid was

FIG 2. Paired observations of cardiac output during standard CPR (STD) and CPR with interposed abdominal compressions (IAC) in 10 dogs. Each data point represents mean of five trials in same animal.
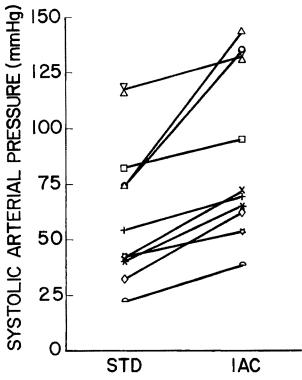
FIG 3. Paired observations of systolic brachial arterial pressure during standard CPR (STD) and CPR with interposed abdominal compressions (IAC) in 10 dogs. Each data point represents mean of five trials in same animal.
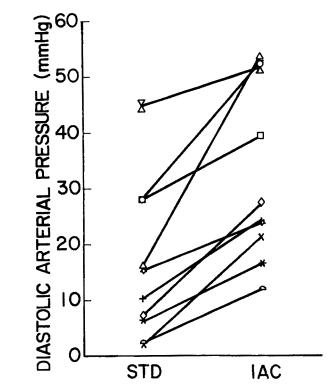
FIG 4. Paired observations of diastolic brachial arterial pressure during standard CPR (STD) and CPR with interposed abdominal compressions (IAC) in 10 dogs. Each data point represents mean of five trials in same animal.

FIG 5. Paired observations of central arteriovenous pressure difference during standard CPR (STD) and CPR with interposed abdominal compressions (IAC) in 10 dogs. Each data point represents mean of five trials in same animal.

observed in three of the 10 animals and intramesenteric hemorrhages were observed in one animal; such findings were not considered serious in these heparinized animals. Liver laceration never occurred.

Discussion

The addition of interposed abdominal compression to standard CPR greatly improves blood pressure and blood flow in both the large dog and the small dog model of cardiopulmonary arrest. We have speculated that the thoracic pump mechanism for generating blood flow is more important in large animals, whereas the traditional cardiac pump mechanism is more important in smaller animals (6, 9). If so, one can conclude that IAC-CPR is effective in improving hemodynamics caused by either mechanism. The increase in arterial pressure during IAC-CPR is clearly not an artifactual transmission of pressure from the abdomen to the thorax, as both the diastolic arteriovenous pressure difference and the total blood flow improve.

The improvement in arterial pressure during the diastolic phase (release of chest compression) and in central arteriovenous pressure difference during IAC-

CPR is significant in that it is likely to enhance coronary perfusion. Coronary flow during standard CPR is reduced at least in proportion to cardiac output (17) and perhaps even more (18, 19), but is essential for return of cardiac function and survival (20). Quite possibly IAC-CPR offers an especially effective means of increasing coronary flow, both by improving total flow and by favorably altering the distribution of aortic run-off during chest recoil.

We hypothesize that the hemodynamic effects of interposed abdominal compression include pump priming and aortic counterpulsation. Abdominal compression, like atrial contraction in the normally beating heart, may encourage blood into the main pumping chamber, which during CPR may include the thorax as a whole, the cardiac ventricles, or both (9). Moreover, diastolic abdominal pressurization must, to some degree, improve the distribution of blood flow, favoring the brain and the heart as compared with kidneys, intestines, and lower extremities. To the extent that aortic counterpressure occurs, the effect is similar to surgical cross-clamping of the aorta in an extreme hemodynamic emergency. However, total cardiac output is dramatically increased by al-

ternate abdominal compression, suggesting an equally important effect of IAC-CPR on the abdominal venous vasculature.

Previously, Harris and associates (21) found that continuous manual compression of the abdomen increased carotid flow by two thirds, a degree of flow augmentation similar to that in the present study. However, these authors did not recommend manual compression of the upper abdomen during CPR because lacerations of the liver were noted in two of six dogs. In 1971, Redding (22) demonstrated improved carotid arterial flow and survival in experimental CPR with continuous abdominal compression by a blood pressure cuff secured around the mid-abdomen, while observing no greater incidence of liver damage during CPR with continuous abdominal binding than in similarly resuscitated animals without abdominal binding. Recently Bircher, Safar, and Stewart (23) reported a study of experimental CPR in dogs in which a pressure suit was continuously inflated around the legs and abdomen. They found "no major lacerations of the liver" in 12 dogs receiving this treatment, which did increase arterial pressure and carotid flow at least transiently. Rosborough and co-workers (24) have reported that synchronous abdominal compression and lung inflation can produce effective artificial cough-CPR in dogs with no evidence of visceral trauma.

We suggest that the small but significant incidence of liver laceration with continuous abdominal binding is due to entrapment of the liver by the rib cage as the chest is compressed. However, during interposed as opposed to continuous abdominal compression, the liver is allowed to recede at the time the chest is compressed, so that entrapment and laceration of the liver is less likely. We have observed such back-and-forth motion of the liver and diaphragm fluoroscopically during IAC-CPR in two dogs, using techniques previously described (25). Although it is certainly possible that excessively rough or vigorous abdominal compression could traumatize the liver or spleen, we believe that central abdominal compression over a large area with 120 to 150 mm Hg pressure, which is adequate to augment perfusion, is much less than that required to produce blunt trauma.

Abdominal counterpressure during CPR did not cause regurgitation in the animals in this study, but it is fitting to mention the possibility of provoking regurgitation and aspiration by IAC-CPR. In our animals a tracheal tube was securely in place, and gastric insufflation did not occur. Gastric distension is a common sequela of mouth-to-mouth ventilation in

humans (26), and abdominal pressure may induce vomiting after the stomach is distended with air (1). However, one may speculate that if the IAC technique were used consistently from the beginning of resuscitation, gastric distension might be entirely prevented by the abdominal counterpressure. In the technique described in this study, abdominal pressure was applied and maintained throughout ventilation, in exact counterpoint to the rhythm of chest compression. Quite likely this technique would prevent passage of air into the stomach during mouth-to-mouth rescue breathing in man. The most probable situation in which interposed abdominal compressions might induce regurgitation would be if the technique were added after a period of conventional CPR—as might occur after others come to the aid of a lone rescuer. As there are no good animal models for mouth-to-mouth ventilation, this issue will have to be settled by clinical experience.

In summary, the addition of intermittent abdominal compression to standard CPR appears to be a simple, safe, and effective means of improving perfusion during initial resuscitative efforts. The technique appears to be applicable to field CPR by basic rescuers and emergency medical personnel. It requires no extra mechanical equipment, and, if proven effective in human trials, could be easily incorporated into existing training programs for lay rescuers and hospital personnel.

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Epidural Meperidine-Bupivacaine for Obstetric Analgesia

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BARAKA, A., MAKTABI, M., AND NOUEIHID, R. Epidural meperidine-bupivacaine for obstetric analgesia. Anesth Analg 1982;61:652–6.

In 13 full-term primipara in active labor an initial single dose of preservative-free meperidine (100 mg) diluted in 10 ml of saline was injected epidurally (L2–3). In another 13 full-term parturients in active labor, 10 ml of bupivacaine 0.25% was used. Pain was scored by the linear analog scale. Onset of analgesia was 5.3 ± 2.8 minutes following administration of meperidine, and 12.9 ± 6.9 minutes following bupivacaine ($p < 0.01$). Pain score decreased to 0 in 12 of 13 patients following meperidine administration and in six of 13 patients following bupivacaine ($p < 0.01$). Satisfactory analgesia lasted 160.8 ± 90.3 minutes following meperidine, and 103.5 ± 42 minutes following bupivacaine administration ($p < 0.01$). Subsequent supplementation by intermittent doses of 10 ml of bupivacaine 0.25% was more effective and less frequent following meperidine than following bupivacaine administration. Maternal sedation, nausea, and itching occurred frequently following administration of epidural meperidine, whereas hypotension, numbness, and motor dysfunction followed bupivacaine. In neither group was significant respiratory depression observed. All parturients delivered vaginally, 288 ± 212.6 minutes following meperidine and 348 ± 195.8 minutes following bupivacaine administration ($p > 0.05$); the neonates showed normal Apgar scores and neurobehavioral responses. Epidural meperidine, supplemented by subsequent bupivacaine as indicated, provides maternal sedation and satisfactory analgesia, and it diminishes the requirements of bupivacaine supplementation. The technique is advantageous in the parturient primipara.

INTRATHECAL injection of morphine has been shown to produce long-lasting obstetric analgesia in the parturient primipara (1). In contrast, epidural morphine has failed to relieve labor pain (2, 3). This has been attributed to the increased vascularity of the epidural space in pregnancy which may result in rapid systemic absorption of the epidurally injected morphine (2). Meperidine, being more lipophilic than the hydrophilic morphine (4), can diffuse readily across the dura into the subarachnoid space (5) and hence may be successful in providing analgesia in the parturient (6, 7).

In the present clinical trial, we investigated the obstetric analgesic effect of epidural meperidine-bupivacaine sequence in a group of parturient primiparas, and compared the analgesic effect with that achieved in patients managed by epidural bupivacaine alone. We also compared the progress of labor in the two groups, and report the side effects on both the mother and the newborn.

Methods and Materials

This investigation was approved by the Human Studies Committee. The protocol was explained to each participating parturient and her informed consent was obtained. Observations were carried out on 26 full-term primiparous women. All parturients were admitted to the delivery suite in active labor and all had cephalic presentations. An intravenous infusion of lactated Ringer's solution was started. When the cervix was fully effaced and 4 cm dilated, parturients were positioned in the left lateral position and a 17-gauge Tuohy needle was inserted in the second lumbar interspace. An epidural catheter was then threaded for 3 to 5 cm within the epidural space.

In 13 parturients whose ages ranged from 18 to 24 years (mean = 20 years, SD = 2.5), epidural meperidine followed by subsequent injection of bupivacaine as indicated was used, whereas the other 13 parturients, whose ages ranged from 17 to 25 years (mean = 21 years, SD = 1.9), served as a control group receiving bupivacaine only. In patients given meperidine, an initial single dose of preservative-free me-

peridine, 100 mg, diluted in 10 ml of preservative-free normal saline, was injected epidurally. The control group received 10 ml of plain bupivacaine 0.25%. Following epidural injection of either solution, the parturient was positioned in a 30° head-up tilt for 30 minutes and was then encouraged to lie in the left lateral position. In both groups, analgesia was subsequently supplemented by intermittent doses of 10 ml of bupivacaine 0.25%.

Continuous recording of uterine contractions and fetal heart rate was obtained throughout labor using a Hewlett-Packard cardiotocograph. The following were observed and recorded.

Obstetric Analgesia

Pain was scored according to the visual linear analog (8), which has been suggested as a reliable method of evaluating severe pain such as that of labor (1, 8). The base line labor pain intensity was scored before the epidural injection. After epidural administration of meperidine or bupivacaine, the pain score was assessed with every uterine contraction. The onset time of analgesia was defined as the time from epidural injection until the first nonpainful contraction, whereas the duration of analgesia was defined as the time from the epidural injection until the parturient requested further pain relief.

Progress of Labor

Progress of labor was monitored by continuous external cardiotocography and by repetitive vaginal determinations of cervical dilation. After full cervical dilation and complete descent of the presenting vertex, all parturients were delivered vaginally using episiotomy and low forceps extraction.

Fetal heart rate was continuously monitored externally by the Hewlett-Packard cardiotocograph. At birth, the neonates were assessed by the use of the Apgar score. In the nursery, a neurobehavioral assessment (9) was made 6 to 12 hours after delivery by a neonatologist who was unaware of the anesthetic management. The following variables were scored: resistance against passive motion, rooting, sucking, Moro response, habituation to light, placing, and alertness. The neurobehavioral response was scored as absent, weak, or normal.

Maternal Side Effects

Maternal sensory (pinprick sensation), motor (reflexes and motor power), and autonomic (blood pres-

sure and pulse rate) function, as well as respiratory rate, were recorded at 5-minute intervals following each epidural injection. Also, the occurrence of other side effects such as somnolence, nausea, and itching were recorded and rated as absent, mild, moderate, or severe.

Student's t-test was applied to compare data related to analgesia and progress of labor; $p < 0.05$ was considered statistically significant.

Results

Obstetric Analgesia

In all parturients, epidural injection was performed when the cervix was fully effaced and 4 cm dilated. The mean time of onset of analgesia was 5.3 minutes (SD = 2.8) in patients given meperidine, and 12.9 minutes (SD = 6.9) in patients given bupivacaine (p < 0.01). Twelve of the 13 parturients receiving meperidine had zero pain scores, whereas only six of the 13 receiving bupivacaine reached zero scores (p < 0.01). The mean duration of analgesia was 160 minutes (SD = 90.3) following meperidine, and 103 minutes (SD = 42) following bupivacaine administration (p < 0.01). In Fig 1 the mean pain scores versus time following the epidural administration of meperidine and bupivacaine are compared.

In both groups of parturients, analgesia was subsequently supplemented by intermittent doses of 10 ml of bupivacaine 0.25%. Following meperidine, one to four supplementary doses (mean 2.38 doses, SD = 1.0) were required. On the other hand, following bupivacaine 4.5 doses (SD = 1.2), including the initial dose, were required (p < 0.001); three parturients of
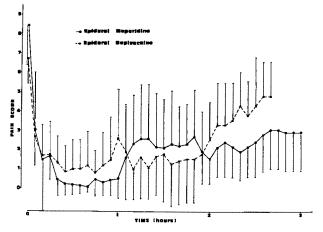
FIG 1. Mean pain score (±SD) versus time in two groups of parturients. Zero time denotes time of epidural injection of meperidine or bupivacaine.

this group developed tachyphylaxis following the repeated administration of bupivacaine.

Progress of Labor

There was no significant difference in the progress of labor in the two groups. Full cervical dilation up to 10 cm was reached within a mean time of 229 minutes (SD = 201) in patients given meperidine, and 284 minutes (SD = 178.8) in those given bupivacaine (p > 0.05). Mean cervical dilation as a function of time in the two groups of parturients is depicted in Fig 2. The mean duration of the second stage of labor (i.e., time between full cervical dilation and delivery) was 58.8 minutes (SD = 43.4) when meperidine was injected, and 66.1 minutes (SD = 42.4) when bupivacaine was used (p > 0.05).

Newborn Side Effects

External monitoring of the fetal heart rate by cardiotocography showed a normal pattern with no loss of beat-to-beat variability in any case, except for one fetus in the meperidine group who showed transient late deceleration. At birth, newborns of both groups cried immediately and had Apgar scores of 7 to 9 at 1 minute and 8 to 10 at 5 minutes. In the nursery, all newborns showed a normal neurobehavioral response.

Maternal Side Effects

Following epidural meperidine, none of the parturients had any alteration in the motor power or reflexes, whereas pinprick testing showed patchy hy-
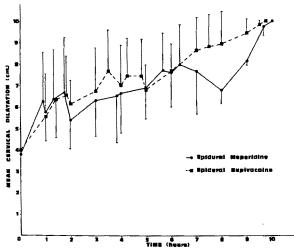
FIG 2. Mean (±SD) cervical dilation versus time in two groups of parturients. Zero time denotes time of epidural injection of meperidine or bupivacaine.

poalgesia. On the other hand, epidural bupivacaine always resulted in numbness, motor weakness, decreased motor reflexes, and marked decrease of pinprick sensation to a level ranging between T8 and T11. Stable pulse rates and blood pressures were observed in all parturients given meperidine, whereas two of the patients given bupivacaine developed hypotension and bradycardia that required treatment.

Systemic maternal side effects were observed without asking leading questions. Following meperidine administration, all parturients became sedated and sleepy. Itching was observed in seven parturients but was always mild, transient, and localized to the nose and face. Also, nausea occurred in three parturients, whereas nausea associated with occasional vomiting occurred in another five cases. Following bupivacaine administration, only two parturients became sleepy, vomiting occurred in four parturients, and shivering was observed in six parturients.

In neither group was significant respiratory depression clinically observed. Resiratory rate ranged between 18 to 25 breaths per minute before epidural injection, and was only decreased to 16 breaths per minute in three parturients given meperidine. Maternal side effects in the two groups are compared in the Table.

Discussion

Intrathecal injection of morphine has been shown to produce selective obstetric analgesia in the parturient primipara without motor or autonomic side effects (1). This has been attributed to the action of morphine on the opiate receptors located in the substantia gelatinosa of the dorsal horn of the spinal cord (10). Morphine, which is hydrophilic, has a low lipid partition coefficient (4), hence it slowly reaches the receptor sites, resulting in a delayed onset of analgesia. The hydrophilic character of morphine may also explain its retention in the spinal cord and its slow

TABLE

Side Effects Observed in Two Groups of Parturients

Side effects	Meperidine (N = 13)	Bupivacaine (N = 13)	p
Somnolence	13	2	<0.001
Nausea or vomiting	8	4	>0.05
Itching	7	0	<0.001
Shivering	0	6	<0.01
Slowing of respiratory rate	3	0	>0.05
Hypotension	0	2	>0.05
Numbness and heaviness of limbs	0	13	<0.001

release into the systemic circulation resulting in a prolonged effect (1).

In contrast with the effective and long-lasting obstetric analgesia achieved by intrathecal morphine (1), epidural morphine fails to relieve labor pain (2, 3). This has been attributed to the increased vascularity of the epidural space in the parturient which may result in rapid absorption into the systemic circulation of the epidurally injected morphine so that effective concentrations of morphine in the cerebrospinal fluid (CSF) are not reached (2). Meperidine, being much more lipophilic than morphine (4), diffuses readily across the dura into CSF (5). This can explain the effective analgesia that followed epidural injection of meperidine in our parturient primipara. The lipophilic character of meperidine can also explain the rapid onset and relatively short duration of the resulting analgesia.

Similar to our experience with intrathecal morphine (1), epidural meperidine, although it relieves the visceral type of labor pain, fails to block completely pinprick sensation and similar sharp localized pain such as that induced by episiotomy or by stretching of the vulva and perineum. Morphine or its analogs are powerful suppressors of visceral pain and have little or no effect on pricking sensation (11). In addition to a selective spinal action, epidural meperidine may also produce analgesia secondary to systemic absorption, and by nerve conduction, block due to its local anesthetic property (7).

The analgesic effect of meperidine in our parturients was associated with a high incidence of somnolence, nausea, and itching. These side effects can be explained by systemic absorption of the epidurally injected meperidine. Systemic absorption of epidural meperidine occurs readily in the parturients (7) and can thus not only supplement its spinal analgesic effect, but also contribute to its side effects. The somnolence, nausea, and itching following epidural meperidine may be also attributed to its transdural spread into the subarachnoid space and subsequent cephalad spread within the CSF by passive diffusion along a concentration gradient effect to the fourth ventricle and its surrounding brain tissues. Supraspinal spread, however, is probably more important with the hydrophilic morphine than with the lipophilic meperidine (12). The CSF concentrations of highly lipid-soluble compounds rapidly decrease below effective levels because of rapid absorption onto neural elements and rapid elimination from the subarachnoid space (13). On the other hand, serious side effects including delayed respiratory and cardiovas-

cular depression may follow the epidural or intrathecal administration of poorly lipid-soluble drugs such as morphine (12, 14), which will linger in the CSF to be carried wherever the flow may take them (12).

Epidural meperidine provided our parturient primiparas with selective obstetric analgesia and sedation, without any associated numbness, heaviness of lower limbs, or cardiovascular changes. Also, subsequent supplementation with bupivacaine was more effective and less frequently required than in patients initially given bupivacaine. In contrast with epidural meperidine, the onset of analgesia was delayed following bupivacaine and was associated with numbness, heaviness of lower limbs, and occasional hypotension. Also, the degree of analgesia following bupivacaine 0.25% was incomplete in some parturients, and tachyphylaxis developed in two cases following the frequent use of supplementary doses.

Because of the significant systemic absorption of meperidine that can follow its epidural administration in the parturient (7), it is advisable not to use epidural meperidine in repeated doses and to limit its use to an initial single dose followed by subsequent supplementation by small concentrations of bupivacaine. This may minimize the maternal side effects and any possible fetal depression. It also ensures adequate analgesia throughout the different stages of labor including episiotomy and forceps extraction.

In conclusion, epidural meperidine, followed by bupivacaine when necessary, provides adequate maternal sedation and selective obstetric analgesia, and it increases the effectiveness of bupivacaine supplementation. The technique is advantageous in the parturient primipara who is usually anxious and having a prolonged delivery course.

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Pharmacokinetics of Alfentanil in Man

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The distribution and elimination kinetics of alfentanil, a new short-acting analgesic, were studied in five surgical patients. Its behavior, following a bolus injection of 120 µg/ml, was compatible with a three-compartment open-model distribution. The disappearance of the drug from plasma was rapid ($t\frac{1}{2}\pi$ = 3.5 ± 1.3 minutes, $t\frac{1}{2}\alpha$ = 16.8 ± 6.4 minutes) with 96.4% of the drug eliminated from plasma in 1 hour, indicating extensive transfer to the remote peripheral compartment. This was followed by a slower elimination phase with a $t\frac{1}{2}\beta$ of 94 ± 38 minutes. Total volume of distribution was 1.03 ± 0.50 L/kg. Total plasma clearance was 456 ± 155 ml/min. The short analgesic effect of this drug might be attributed to the rapid displacement of the drug from the central and intermediate compartments to the remote peripheral compartment. Approximately 25% of the injected dose was present in the remote peripheral compartment 30 to 60 minutes after alfentanil administration. As the return of drug from this peripheral to the central compartment is slower than the elimination rate of the drug, it could be the rate-limiting step in the elimination of alfentanil from the body.

Key Words: ANALGESICS: alfentanil; PHARMACOKINETICS: alfentanil.

RECENT PUBLICATIONS (1-3) propose the use of high-dose fentanyl anesthesia to suppress surgical stress. Although adequate depth of anesthesia is provided, a prolonged and recurrent respiratory depression may occur during the recovery period following anesthesia and surgery depending on the pharmacokinetic properties of fentanyl (4-6). The high-dose analgesic anesthesia technique would be more acceptable with potent narcotics showing a faster elimination from the body.

Alfentanil (R 39209, Janssen Pharmaceutica) is a morphine-like analgesic with a potency and duration of action one third that of fentanyl and with a wide margin of safety (7, 8). Preliminary clinical studies in man (9-11) indicate that alfentanil, when administered for surgical anesthesia, is associated with minimal cardiovascular depression or alteration of activity of the autonomic nervous system and produces a

short-lasting respiratory depression. This study reports the pharmacokinetics of alfentanil in surgical patients receiving a single intravenous dose of alfentanil.

Methods

The experimental protocol was approved by the Commission for Medical Ethics of the University. Informed consent was obtained from five healthy female patients scheduled for routine general surgery. None had clinical or biochemical evidence of hepatic or renal disease. Patient data are shown in Table 1. Each patient was premedicated with diazepam, 10 mg, and atropine sulfate, 0.5 mg, intramuscularly 45 minutes before anesthesia. Anesthesia was induced with etomidate, 0.2 mg/kg IV and maintained with nitrous oxide-oxygen and an inspired concentration of 0.6% to 1% halothane in a semiclosed circuit. Two patients received a single dose of succinylcholine, 50 to 75 mg, to facilitate tracheal intubation. Ventilation was mechanically controlled throughout the surgical procedure and adjusted to maintain arterial P_{aCO_2} levels between 4.6 and 5.0 kPa (34.5 to 37.5 mm Hg). Intravenous fluids were administered at a rate of 10 ml/kg/hr and surgical blood loss was replaced with equal amounts of whole blood. Alfentanil was given as a bolus (120 µg/kg) in 30 seconds into an antecubital vein before surgical incision at a time when

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TABLE 1

Data for Five Female Patients*

Patient	Age	Weight	Height	BSA*	Alfentanil dose	Operation
	yr	*kg*	*cm*	*m²*	*mg*	
1 (D.T.)	36	52	154	1.51	6.24	Thyroidectomy
2 (V.V.)	55	72	162	1.84	8.64	Hysterectomy
3. (D.R.)	48	58	161	1.64	7.08	Thyroidectomy
4 (V.A.)	33	59	159	1.64	7.08	Thyroidectomy
5 (T.M.)	43	46	150	1.40	5.52	Splenectomy
Av ± SD	43 ± 9	57.4 ± 9.7	157 ± 5	1.61 ± 0.16	6.91 ± 1.17	

* Abbreviation used is: BSA, body surface area.

blood pressure, heart rate, and blood-gas values had stabilized following tracheal intubation. Heparinized arterial blood samples were withdrawn from the arm opposite the site of injection just before and 2, 5, 10, 15, 30, 45, 60, 90, and 120 minutes after injection, then hourly for an additional 4 hours. Samples were immediately centrifuged and plasma aliquots were stored at −20°C until assay of alfentanil.

Plasma alfentanil levels were determined by gas-liquid chromatography with specific thermionic detection described in detail elsewhere (12). Plasma levels of alfentanil from each patient were fitted to a three-compartment open-mamillary model using nonlinear least-squares regression analysis. Apparent volume of distribution $(V_{d\beta})$, volume of the central compartment (V_c), half-lives of the distribution $(t\frac{1}{2}\alpha)$ and elimination $(t\frac{1}{2}\beta)$ phases, total plasma clearance (Cl_p), first-order rate constants for drug transfer between compartments $(k_{12}, k_{21}, k_{13}, k_{31})$, and the elimination rate constant (k_{10}) were calculated in the usual manner (13). In this model, drug elimination was assumed to occur via the central compartment with first-order kinetics.

As a first approximation, the hepatic extraction ratio of a drug cleared from the body solely via hepatic metabolism was estimated using the following equation:

$$E_H = \frac{Cl_{blood}}{Q_H}$$

where E_H represents the hepatic extraction ratio, Cl_{blood} the whole blood clearance (ml/min) calculated as the product of plasma clearance and the plasma to blood concentration ratio, and Q_H the hepatic blood flow (ml/min).

Results

Time Course of Plasma Concentration

Following an intravenous bolus injection of alfentanil, there was a rapid decline of plasma concentra-
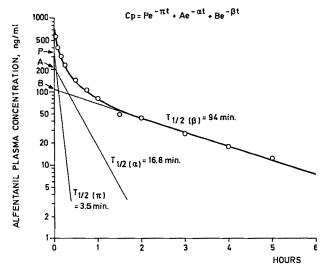
Fig 1. Mean plasma alfentanil concentrations in five subjects following 0.120 mg·kg⁻¹ intravenous injection.

tion during the first 15 minutes. Within 60 minutes, 96.4% of the dose was eliminated from plasma (Fig 1). The individual data of the patients are shown in Table 2. In two patients a secondary increase of the plasma alfentanil concentration was observed at 120 minutes. In these patients, the blood sample was taken just following extubation. The plasma level data of the patients were fitted to a triexponential equation $C_p(t)$ = $P \cdot e^{-\pi t} + A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$ describing a three-compartment open-model in which alfentanil is introduced directly into the central compartment (Fig 2). In Table 3 are summarized the nonlinear least-squares estimates for the three-compartment model parameters P, π, A, α, B, β, together with the model-derived pharmacokinetic parameters calculated for each patient. The disappearance from plasma occurred rapidly during the distribution phase (mean half-lives of 3.5 ± 1.3 minutes for the central compartment and 16.8 ± 6.4 minutes for the intermediate compartment). The slow component (elimination phase) had a mean half-life of 94 ± 38 minutes. The time course of the apparent concentrations expressed as fractions of the

TABLE 2

Plasma Levels of Alfentanil following Intravenous Bolus Injection of 0.120 mg·kg^{-1}

Time	Patients receiving alfentanil (ng)/milliliter of plasma					
	D.T.	V.V.	D.R.	V.A.	T.M.	Mean ± SD
min			*ng/ml*			
2	533.0	631.0	599.0	449.0	612.0	565 ± 74.5
5	398.0	476.0	339.0	360.0	423.0	399 ± 53.9
10	263.0	396.0	243.0	281.0	329.0	302 ± 61.3
15	216.0	303.0	161.0	225.0	241.0	229 ± 51.1
30	127.0	201.0	124.0	119.0	156.0	145 ± 34.3
45	81.6	171.0	74.7	82.8	118.0	106 ± 40.3
60	55.2	130.0	59.7	52.8	109.0	81.3 ± 35.7
90	32.5	85.1	37.0	21.7	55.6	48.7 ± 28.1
120	21.1	105.0	28.2	29.3	35.6	43.8 ± 34.6
180	10.2	77.7	14.0	19.8	12.1	26.8 ± 28.7
240	7.55	56.5	10.9	7.87	5.56	17.7 ± 21.8
300	5.10	43.8	6.85	4.03	2.00	12.4 ± 17.7
360	3.08	—	4.84	—	≤1.0	—
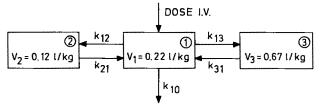
FIG 2. Three-compartment open model for alfentanil pharmacokinetics.

alfentanil dose appearing in the three compartments of the model is described in Fig 3.

Tissue Accumulation and Clearance

The mean volume of the central compartment was estimated at 12.3 (± 2.3) L and the total apparent volume of distribution reached 1.03 (± 0.50) L/kg. Mean total plasma clearance was estimated to be 456 (± 155) ml/min. As the alfentanil plasma to blood concentration ratio is 1.59 (W. Meuldermans, Janssen Pharmaceutica, Beerse, personal communication, 1981), the mean total body clearance in terms of whole blood was 730 ml/min. The estimated hepatic extraction ratio for alfentanil thus yielded 0.49 assuming a mean hepatic blood flow of 1500 ml/min (14).

One patient (V.V.) showed a lower clearance of the drug than did the other patients. Although this patient was slightly obese, the kinetic parameters still indicated rapid equilibration of the drug between the central and the remote peripheral compartments (k_{31}/k_{13} = 0.72) and a high amount of the drug available for clearance in the central compartment (β/k_{10} = 31.2% of dose). The hepatic extraction ratio in this patient was estimated as 0.20, suggesting possible saturation of the metabolic clearance mechanism or liver insufficiency.

Discussion

This study investigated the distribution and elimination of a standard alfentanil dose used in clinical anesthesia. An induction dose of 4.1 mg of alfentanil has been reported to produce unconsciousness within 50 seconds in surgical patients (10).

The plasma concentration decay curves in our patients could be adequately described by a three-compartment open-mamillary model. Our choice for using a three-compartment model rather than a two-compartment model for the description of the time-dependent plasma curves for alfentanil in the group of patients studied is based on the fact that the goodness of fit, as indicated by the sum of weighted squares of deviation between observed and predicted concentration values, was significantly better for the three-exponential model. Significance was tested using the F-ratio test (15). This pharmacokinetic model has been used previously for fentanyl (16–18) although some authors reported two-compartment model pharmacokinetics (19–21). This difference in opinion could be related to differences in blood sampling frequency appearing in the various experimental protocols.

The distribution of alfentanil is rapid as the half-lives of the early exponential phases (t½π and t½α), considered to reflect distribution from the central and rapidly equilibrating intermediate peripheral compartments, averaged 3.5 and 16.8 minutes, respectively. This is consistent with rapid penetration into brain tissue, manifested by the rapid onset of unconsciousness, followed by rapid displacement of the drug to a slower remote peripheral compartment.

The extent of distribution is indicated by the large

TABLE 3

Pharmacokinetic Parameters for Alfentanil in Individual Patients*

Parameter (units)	D.T. (52 kg)	V.V. (72 kg)	D.R. (58 kg)	V.A. (59 kg)	T.M. (46 kg)	Mean ± SD
P (ng/ml)	415	387	642	139	330	383 ± 181
A (ng/ml)	269	141	161	370	168	222 ± 97
B (ng/ml)	35	188	44	109	206	116 ± 79
π (min^{-1})	0.237	0.127	0.243	0.309	0.183	0.220 ± 0.068
α (min^{-1})	0.034	0.043	0.027	0.072	0.058	0.047 ± 0.018
β (min^{-1})	0.007	0.005	0.006	0.011	0.015	0.009 ± 0.004
$t\frac{1}{2}\pi$ (min)	2.9	5.5	2.9	2.2	3.8	3.5 ± 1.3
$t\frac{1}{2}\alpha$ (min)	20.6	16.2	25.5	9.7	11.9	16.8 ± 6.4
$t\frac{1}{2}\beta$ (min)	104	141	114	64	46	94 ± 38
V_c (L)	11.7	11.7	9.9	16.2	11.9	12.3 ± 2.3
$V_{d\beta}$ (L)	83.9	38.4	87.7	50.4	30.3	58.1 ± 26.3
V_c (L/kg)	0.23	0.16	0.17	0.27	0.26	0.22 ± 0.05
$V_{d\beta}$ (L/kg)	1.61	0.53	1.51	0.85	0.66	1.03 ± 0.50
Plasma clearance (ml/min)	557	188	534	544	458	456 ± 155
Body clearance (ml/min·kg)	10.7	2.6	9.2	9.2	10.0	8.3 ± 3.3
k_{10} (min^{-1})	0.048	0.016	0.054	0.034	0.038	0.038 ± 0.015
k_{12} (min^{-1})	0.087	0.030	0.113	0.015	0.042	0.057 ± 0.041
k_{21} (min^{-1})	0.118	0.074	0.077	0.290	0.116	0.135 ± 0.089
k_{13} (min^{-1})	0.015	0.032	0.023	0.028	0.024	0.024 ± 0.007
k_{31} (min^{-1})	0.009	0.023	0.010	0.024	0.036	0.020 ± 0.011

* Abbreviations used are: P, π, A, α, B, β, three-compartment model parameters; $t\frac{1}{2}\pi$, $t\frac{1}{2}\alpha$, $t\frac{1}{2}\beta$, half-lives of distribution and elimination phases; V_c, volume of central compartment; $V_{d\beta}$, volume of distribution; k_{12}, k_{21}, k_{13}, k_{31}, first order rate constants for drug transfer between compartments; k_{10}, elimination rate constant.
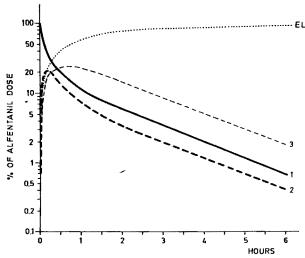
FIG 3. Fractions of alfentanil dose in various compartments. 1, Central compartment; 2, shallow compartment; 3, deep compartment; EL, fraction of dose eliminated.

total apparent volume of distribution equal to total body weight ($V_{d\beta}$ = 1.03 L/kg), but much less than for fentanyl (16). However, the influence of the hemodynamic effects of anesthesia and surgery on the volume of distribution $V_{d\beta}$ could not be evaluated in our study.

As the binding of alfentanil to plasma proteins averages 92% (W. Meuldermans, Janssen Pharmaceutica, Beerse, personal communication, 1981), the extent of distribution of alfentanil could in fact have been underestimated in our study. Our data indicate a lesser tissue accumulation of alfentanil when compared with fentanyl (16), probably related to lower lipid solubility and higher plasma protein binding (alfentanil 92%, fentanyl 84%).

The rate of constants k_{12}, k_{21}, k_{13}, and k_{31} reflect the rate of distribution of the drug among compartments of the model. The mean ratio of k_{31}/k_{13} of 0.83, reflecting drug movement between the central and remote peripheral compartment, suggests rapid equilibration between these compartments (Fig 3) and may explain the rapid decline of alfentanil plasma levels through extensive uptake of the drug by these tissues corresponding to approximately 25% of the dose (Fig 3). The short duration of action of alfentanil might thus be explained by the rapid redistribution of the drug from the central and intermediate compartments to the remote peripheral compartment (k_{21} > k_{13}). Fluctuations in plasma alfentanil levels during the elimination phase were observed in two patients. This may represent mobilization of drug tissue depots by increased perfusion at the time of cessation of anes-

thesia. Similar findings had been observed for fentanyl (20) and meperidine. The elimination rate constant k_{10} was on the average 2 times greater than k_{31}, the rate of return of the drug from the remote peripheral compartment. The mean ratio of β/k_{10} of 0.24 indicates that 24% of the alfentanil in the body is in the central compartment available for elimination at any time. As the rate constant k_{31} was less than the elimination rate constant k_{10}, the re-uptake into plasma from remote peripheral tissues could be the rate-limiting step in the elimination of alfentanil. The apparent elimination half-life of alfentanil averaged 94 minutes, also much shorter than for fentanyl (16). Preliminary studies have shown the metabolism of alfentanil to occur primarily in the liver with O-dealkylation and N-dealkylation as the main metabolic pathways. The metabolites of alfentanil have no pharmacologic activity (8). Based on findings from animal data showing a urinary excretion of only 1% of the injected dose of alfentanil in uncharged form, the main route of elimination thus appears to be hepatic clearance, which can be estimated to be 722 ml/min. However, this assumes that the hepatic blood flow is not significantly decreased by the halothane-nitrous oxide anesthesia. As the mean duration of anesthesia included 2 hours of the total 6-hour test period, an anesthetically induced decrease in total hepatic blood flow could indeed diminish the estimated hepatic clearance. But even with a 30% halothane-induced reduction in total hepatic blood flow (22), the hepatic extraction ratio of alfentanil would still reach 0.70. This suggests the hepatic extraction ratio is only moderately influenced by changes in hepatic blood flow.

In conclusion, the pharmacokinetic data are consistent with rapid distribution of alfentanil within a central and intermediate peripheral compartment, including the brain and highly perfused organs, followed by a displacement to a remote peripheral compartment. These findings explain the rapid onset and short duration of action of the drug in man. Therefore, alfentanil is rapidly eliminated mainly by biotransformation in the liver due to efficient hepatic extraction.

ACKNOWLEDGMENT

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Acid-Base Status of Diabetic Mothers and Their Infants following Spinal Anesthesia for Cesarean Section

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Acid-base status and Apgar scores were evaluated in 10 rigidly controlled insulin-dependent diabetic mothers and 10 healthy nondiabetic control women having spinal anesthesia for cesarean section. Dextrose-free intravenous solutions were used for volume expansion before induction of anesthesia, and hypotension was prevented in all cases by prompt treatment with ephedrine. There were no significant differences in the acid-base values between the diabetic and nondiabetic mothers and the infants of the diabetic and control group. Apgar scores were also similar in the two groups. If maternal diabetes is well controlled, if dextrose-containing solutions are not used for maternal intravascular volume expansion before delivery, and if maternal hypotension is avoided, spinal anesthesia can be used safely for diabetic mothers having cesarean section.

PREGNANCY in the diabetic patient is associated with increased hazard to mother and fetus. Cesarean section is frequently required in this high risk group. In a previous investigation (1), we noticed lower umbilical arterial pH values in infants of diabetic mothers having spinal anesthesia for cesarean section than in infants whose diabetic mothers received general anesthesia (7.20 vs 7.28). Possible mechanisms suggested to explain this difference included: (a) The glycogen-rich placenta of diabetic parturients might contribute lactate to fetal blood under conditions of relative hypoxia, e.g., decreased uterine blood flow which may occur during maternal hypotension associated with spinal anesthesia (2). (b) Fetal lactic acidemia might occur due to hypoxia

(secondary to maternal hypotension) in presence of hyperglycemia following acute volume loading with dextrose-containing solutions (3). (c) Transplacental movement of insulin into fetuses of uncontrolled diabetic parturients may increase fetal glucose uptake, increase oxidative utilization of glucose by the fetus, and reduce fetal arterial oxygen content in the human, as has been demonstrated in sheep (4).

The present study was designed to assess the effectiveness of (a) strict regulation of maternal blood glucose levels to maintain them between 80 and 90 mg/dl, (b) acute intravenous volume loading immediately before the induction of spinal anesthesia with a dextrose-free solution, and (c) avoidance of maternal hypotension during anesthesia in improving the neonatal acid-base values in this special group of patients.

Methods

Twenty parturients scheduled for elective primary or repeat cesarean section at term were selected at random. Ten were controlled insulin-dependent diabetic mothers (mean preoperative fasting blood glucose level 86 ± 4 mg/dl); 10 were healthy nondiabetic women who served as control patients. Diabetes was

classified according to the criteria of White (5) (class B = 4, class C = 3, class D = 2, class F = 1).

An intravenous infusion of Ringer's lactate solution was established and at least 1500 ml was administered 15 to 30 minutes before induction of spinal anesthesia. Maternal base line blood pressure was measured after placing the patients in a left lateral position with a 15° tilt using a blanket roll under the right side and hip to prevent aortocaval compression. All dural punctures were performed with the patient in the right lateral decubitus position. Tetracaine, 0.8 to 0.9 ml, of a 1% solution mixed with 0.8 to 0.9 ml of a 10% dextrose solution, was injected through a 26-gauge spinal needle at the L2-3 interspace to provide spinal anesthesia. Left uterine displacement was accomplished on placing the parturient on her back after injection of tetracaine by means of a blanket roll under her right side. Sprague (6) has demonstrated better distribution of a hyperbaric local anesthetic solution with this technique of positioning the patient after induction of spinal anesthesia. Bilateral sensory levels of T2-4 were observed in all parturients and were adequate for surgery in all cases. Oxygen (6 L/min) was administered via face mask from the time of induction of spinal anesthesia until delivery of the baby. Maternal electrocardiograms were continuously monitored. Blood pressure was measured by sphygmomanometry at 30-second intervals for the first 15 minutes and every 3 minutes thereafter. Intravenous ephedrine was given in increments of 10 mg if and when a decrease of 10 torr in base line systolic pressure was detected.

Time from the start of the injection of tetracaine to the completion of delivery was recorded in minutes and seconds as induction-delivery interval. The time from the first uterine incision to the delivery of the baby was recorded in seconds as the uterine incision-delivery interval.

At delivery, samples of maternal radial arterial blood were collected, as well as samples of umbilical arterial and venous blood from a doubly clamped segment of umbilical cord. Blood gas tensions and pH values were immediately measured in each sample in duplicate with a Radiometer microelectrode system. Base deficit was calculated using the Siggard-Andersen nomogram (7). Apgar scores were determined at 1 and 5 minutes of age by a pediatrician.

Results

Two diabetic parturients were hospitalized 3 weeks before delivery for control of fasting blood glucose levels. However, before surgery, fasting blood glucose

levels were within normal limits (86 ± 4 mg/dl) in all the diabetic mothers.

Comparison of the two groups of mothers revealed no significant differences in maternal age, height, weight, or gestational age (Table 1). Systolic blood pressure did not exceed 130 torr in any parturients within 24 hours of operation, and none of the mothers had systolic pressures of more than 30 torr from base line levels during anesthesia. The total amount of ephedrine administered varied from 10 to 30 mg and was not significantly different between the two groups.

There were no differences in the induction-delivery or uterine-incision delivery intervals in the two groups (Table 1). The acid-base status of the mothers in both groups was normal at delivery (Table 2). There were no significant differences in acid-base status or in blood gas tensions between infants in the control and in the diabetic group. Only one baby in the diabetic group had an Apgar score less than 7 at 1 minute; the rest of the babies had Apgar scores greater than 7 at both 1 and 5 minutes (Table 1).

Discussion

In our two previous studies (1, 8) with diabetic parturients we reported neonatal acidosis while using regional anesthesia. The neonatal acidosis was related to both severity of maternal diabetes and the presence of maternal hypotension. Thalme and Engstrom (9) and Hollmen et al (10) also observed fetal acidosis after cesarean section with epidural anesthesia in diabetic subjects.

The genesis of fetal acidosis in diabetic parturients is complex and several factors have been involved in human and animal experiments.

TABLE 1
Patient Characteristics*

	Diabetic (N = 10)	Control (N = 10)
Maternal age (yr)	28 ± 1	29 ± 1
Maternal height (cm)	160 ± 1.8	162 ± 1.3
Maternal weight (kg)	68 ± 5	71 ± 3
Gestational age (wk)	38 ± 0.1	40 ± 0.1
Infant birth weight (g)	3456 ± 80	3405 ± 113
I-D interval (min)	14 ± 2	15 ± 3
UI-D interval (sec)	110 ± 12	100 ± 10
Apgar score < 7		
1 min	1	0
5 min	0	0

* Values are means ± SE. Abbreviations used are: I-D interval, induction-delivery interval; UI-D internal, uterine incision-delivery interval.

TABLE 2
Acid-Base and Blood Gas Data*

	Diabetic (N = 10)	Control (N = 10)
Maternal artery		
pH	7.40 ± 0.006	7.42 ± 0.01
P_{O_2} (torr)	205 ± 8	200 ± 9
P_{CO_2} (torr)	33 ± 1	33 ± 2
Base deficit (meq/L)	2.7 ± 0.5	1.3 ± 0.6
Umbilical vein		
pH	7.33 ± 0.01	7.35 ± 0.01
P_{O_2} (torr)	32 ± 3	30 ± 1
P_{CO_2} (torr)	48 ± 2	45 ± 2
Base deficit (meq/L)	1.0 ± 0.6	1.5 ± 0.6
Umbilical artery		
pH	7.27 ± 0.01	7.30 ± 0.01
P_{O_2} (torr)	20 ± 2	22 ± 2
P_{CO_2} (torr)	56 ± 2	50 ± 2.5
Base deficit (meq/L)	4 ± 1	3 ± 0.7
Transplacental base deficit difference†	1.4 ± 1	1.7 ± 0.3

* Values are means ± SE.

† Transplacental base deficit difference = (umbilical arterial base deficit) − (maternal arterial base deficit).

The placenta of the ewe has the ability to produce lactic acid (11). The human placenta also produces lactate in vitro, especially under conditions of hypoxia or increased glycogen deposition as in maternal diabetes. Glycogen-rich placentas of diabetic parturients might contribute lactate to fetal blood under conditions of relative hypoxia, e.g., decreased uterine blood flow which may occur during hypotension (2).

Shelley (12) observed increased accumulation of lactate in fetal lambs during periods of hyperglycemia and hypoxia. Bassett and Maddill (13) confirmed these findings but found no evidence to suggest that hyperglycemia was harmful to well-oxygenated sheep fetuses. Robillard et al (14) compared fetal blood gas tensions, pH values, and plasma lactate concentrations at different levels of fetal hyperglycemia in well-oxygenated sheep fetuses. They observed increased fetal plasma lactate and decreased fetal pH values when fetal plasma glucose concentrations were more than 150 mg/dl, although oxygen tensions did not change. However, severe metabolic acidosis occurred when fetal plasma glucose concentrations were more than 300 mg/dl. The mean fetal pH value decreased from 7.38 to 7.18 and the mean P_{O_2} decreased from 24.3 to 20.3 torr.

We have observed high umbilical vein glucose concentrations (>300 mg/dl) after acute maternal volume expansion when dextrose-containing solutions

were used in normal parturients undergoing cesarean section.

Recently, Kenepp et al (3) observed fetal lactic acidemia in normal parturients who received 5% dextrose solutions for hydration before cesarean section. They explained the acidemia on the basis of hypotension, placental insufficiency, and/or increased glycolysis in an oxygen-poor environment. Recently, we observed (15) significantly better fetal acid-base status when maternal systolic blood pressure remained greater than 100 torr, compared with babies whose mothers had frank hypotension (maternal blood pressure less than 100 torr). Using the xenon washout method, Huovinen and co-workers (16) observed a significant decrease of intervillous blood flow associated with maternal hypotension, which can ultimately lead to neonatal acidosis.

Finally, Carson et al (4) observed that chronic infusion of insulin directly into the sheep fetus increased fetal glucose uptake, increased oxidative utilization of glucose by the fetus, and surprisingly, reduced fetal arterial oxygen content. The authors speculated that hyperinsulinemia may increase oxygen consumption, and that fetal hyperglycemia and hyperinsulinemia might result in reduced fetal oxygenation in pregnancies complicated by diabetes.

The possible mechanisms of fetal acidosis in diabetic mothers after spinal anesthesia described above may be closely interrelated. However, it is not realistically possible at the present time to deal with each variable separately. Therefore, in our present study we tried either to prevent or correct the problems that might cause fetal acidosis in the infants of diabetic mothers.

We observed that strict control of maternal diabetes, avoidance of dextrose-containing solutions for acute maternal volume expansion before anesthesia, and prompt treatment of any decrease of maternal blood pressure will maintain neonatal acid-base status at control levels during spinal anesthesia and avoid the development of acidemia which may place the newborn at increased risk.

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Xanthine Oxidase-Induced Lung Injury Inhibits Removal of 5-Hydroxytryptamine from the Pulmonary Circulation

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Cook, D. R., Howell, R. E., and Gillis, C. N.: Xanthine oxidase-induced lung injury inhibits removal of 5-hydroxytryptamine from the pulmonary circulation. Anesth Analg 1982;61:666-70.

We were interested in determining the effect of lung injury initiated by superoxide anions and hydroxyl radicals on removal of 5-hydroxytryptamine (5-HT) and phenylethylamine by the isolated perfused lung. The rate of removal and percentage of removal of these bioamines was determined before and after lung injury initiated by perfusion of the lung with hypoxanthine (HX) and xanthine oxidase (XO) or xanthine oxidase alone for 10 or 30 minutes; free radicals are generated by such treatment. Because of variation in removal of bioamines among lungs of different animals, the effects of lung injury on bioamine removal were determined by calculating the percentage of inhibition of removal using data from the control and test period for each lung. Perfusion of the lung with HX/XO or XO for 10 or 30 minutes significantly inhibited 5-HT removal by 39.5% and 63.3%, respectively. In contrast, only perfusion of the lung for 30 minutes with HX/XO produced inhibition of phenylethylamine uptake (by 54.8%). As uptake of 5-HT is the rate-limiting step in 5-HT removal, these data demonstrate dose (time)-related depression of active 5-HT uptake by free radicals generated in vitro. The rate-limiting step of phenylethylamine uptake, metabolism by monoamine oxidase, is inhibited only by severe lung injury.

Key Words: LUNG: oxygen toxicity, amine uptake; SEROTONIN: pulmonary uptake; OXYGEN: toxicity.

PROLONGED inhalation of oxygen at high partial pressure damages ciliated cells of the airway, type I cells of the alveoli, and interstitial and capillary endothelial cells (1-5). Metabolites of oxygen (e.g., superoxide anions, hydrogen peroxide, hydroxyl radicals, and higher peroxides) rather than oxygen itself are responsible for this damage. Damage to capillary endothelium of the lung with leakage of fluid into the interstitium is an early manifestation of tissue toxicity following prolonged oxygen administration. The metabolic functions of pulmonary endothelial cells capable of modifying the pharmacologic activity of bioamines can be inhibited by prolonged exposure to oxygen. For example, in the early stages of oxygen toxicity the clearance of 5-hydroxytryptamine from the lung is reduced both in vitro (6) and in vivo (7).

To determine the effect of free radical-induced injury on lung metabolic function, we measured the removal of 5-hydroxytryptamine (5-HT) and phenylethylamine (PEA) by the isolated perfused lung following endothelial damage initiated by superoxide anions generated within the pulmonary circulation. Transport of 5-HT into the endothelial cell is an active process (8), whereas removal of PEA occurs by diffusion; both bioamines are metabolized by monoamine oxidases (9, 10). Use of 5-HT and PEA, therefore, allowed us to determine the effect of superoxide anion-induced endothelial damage on both the uptake and metabolism of bioamines.

Methods

Left and right rabbit lungs were independently but concurrently perfused with aerated Krebs-bicarbonate-dextrose solutions in a recirculating system at a constant flow of 10 ml/min via the first branches of

the pulmonary artery as previously described (8, 10–12). Lungs were statically inflated with air. Pulmonary arterial pressure was continuously monitored with a P23b Statham pressure transducer and recorded on a Grass polygraph; the transducer was zeroed at the midlung position.

The following experimental protocol was used: Each lung was perfused for 10 minutes with oxygenated Krebs-Ringer bicarbonate-dextrose solution to clear the lung of blood. After this washout period, lungs were perfused in a recirculating system from a 100-ml reservoir containing 0.1 μM [^{14}C]5-HT or 0.1 μM [^{14}C]PEA in the Krebs-Ringer solution for 21 to 22.5 minutes. The reservoir was sampled at 3-minute intervals for determination of parent compound and metabolite. The residual volume at the end of the perfusion was recorded.

The lung was then perfused (recirculating system) with a 100-ml reservoir containing 0.1 μM hypoxanthine and xanthine oxidase (0.2 units/ml) in Krebs-Ringer bicarbonate solution for 10 or 30 minutes or with xanthine oxidase (0.2 units/ml) without hypoxanthine for 10 or 30 minutes. The residual volume of the second reservoir was noted at the end of the perfusion. Xanthine oxidase with hypoxanthine or other nonspecific substrates generate superoxide anions and hydrogen peroxide as the primary products of the reduction of oxygen. In turn, hydroxyl radicals are generated as a result of the interaction of superoxide anions with hydrogen peroxide (13–16). We confirmed that superoxide anions were generated in this system by demonstrating reduction of ferric cyanide to ferrous cyanide and by demonstrating oxidation of epinephrine to adrenochrome (16–19). In those studies in which superoxide anions were generated for 10 minutes, the lung was perfused for an additional 20 minutes with Krebs-Ringer solution to equalize the total perfusion times.

The lung was then perfused with Krebs-Ringer solution for 2 minutes to remove the hypoxanthine-xanthine oxidase solution and measurement of 5-HT or PEA removal was repeated. The residual volume of this third reservoir was also recorded. The weight gain for each pair of lungs was noted. For experimental purposes, each lung had uptake of a bioamine determined (control value), had a variable injury period, and had the uptake of the same bioamine redetermined (posttreatment value). Thus, each lung served as its own control. Each data point represents the mean value of four lungs.

Biorex 70 columns were used as previously described (11) to separate unchanged 5-HT and PEA

from their deaminated metabolites, 5-hydroxyindolacetic acid, and phenylacetic acid. The parent compound (nmol/ml) and metabolite (nmol/ml) of bioamine were determined at each time period.

Percentage of removal of 5-HT and PEA was calculated at each time period with the aid of a Wang 2200 computer using the relationship:

$$\text{Percentage of removal (\%R)} = \left[\frac{C_o - C_t}{C_o} \right] \times 100$$

where C_o = concentration of 5-HT in reservoir at time = 0, and C_t = concentration of 5-HT in reservoir at time = t). A plot of log concentrations of parent compound against time revealed a linear relationship, which suggested that first-order kinetics were applicable over the period studied. The slope, K_{10}, of the plot of log dose versus time was calculated from a regression analysis. As $Ke = K_{10}/2.303$, the half-life (min) ($t\frac{1}{2}$) was calculated from the relationship $t\frac{1}{2} = 0.693\ Ke$.

Drugs and Isotopes

Xanthine oxidase (grade IV) and hypoxanthine were supplied by Sigma Chemical Co., St. Louis, MO, ^{14}C-5-hydroxytryptamine (56 mCi/mmol) by Amersham Co., Arlington Heights, IL; and ^{14}C-phenylethylamine (6.9 mCi/mmol) was supplied by New England Nuclear, Boston, MA.

Statistical Methods

Statistical differences in the $t\frac{1}{2}$ and percentage of removal of 5-HT or PEA were assessed with a paired t-test. Differences between groups of data were assessed with a one-way analysis of variance.

Results

During the control determination of bioamine uptake and metabolism there was no increase in perfusion pressure and no net transfer of fluid from the reservoir to the lung. In contrast, coperfusion of the lung with hypoxanthine (HX) and xanthine oxidase (XO) or with xanthine oxidase alone for 10 or 30 minutes resulted in a rapid, variable, but unsustained, increase of perfusion pressure followed by a progressive early loss of fluid from the reservoir; the lung visibly enlarged during this period. The mean change in perfusion pressure was 33.6 ± 4.9 (SEM) torr and the mean weight gain was 30.14 ± 2.68 (SEM) g. There was no difference in the weight gain of the lungs after 10 minutes of perfusion with XO (alone or with hypoxanthine) as compared with perfusion for

TABLE 1

Inhibition of 5-Hydroxytryptamine (5-HT) Removal from Pulmonary Circulation after Exposure to Xanthine Oxidase (XO)*

XO substrate	Exposure time to XO	Control		After treatment		Inhibition of removal
		t½	Removal	t½	Removal	
	min	min	%	min	%	%
HX	10	4.7 ± 0.5	94.5 ± 1.1	15.0 ± 2.3†	56.9 ± 9.2†	39.9 ± 9.0
K	10	7.1 ± 0.5	86.4 ± 2.4	22.7 ± 6.4†	53.1 ± 10.8†	39.1 ± 11.4
HX	30	7.0 ± 0.7	84.7 ± 3.1	107.3 ± 57.4†	36.0 ± 8.7†	57.9 ± 4.9
K	30	8.6 ± 0.3	76.8 ± 1.3	173.4 ± 90.0†	23.7 ± 5.4†	69.4 ± 6.7

* Values are means ± SEM; N = 4 for each set. Abbreviations used are: HX, hypoxanthine; K, unknown reductants.
† Different from control value at $p < 0.05$.

TABLE 2

Inhibition of Phenylethylamine Removal from Pulmonary Circulation after Exposure to Xanthine Oxidase (XO)*

XO substrate	Exposure time to XO	Control		After treatment		Inhibition of removal
		t½	Removal	t½	Removal	
	min	min	%	min	%	%
HX	10	8.5 ± 1.6	82.4 ± 4.3	8.7 ± 2.2	78.6 ± 3.7	4.5 ± 1.8
K	10	8.3 ± 1.8	85.9 ± 3.7	8.1 ± 1.5	81.7 ± 2.9	4.6 ± 2.7
HX	30	5.0 ± 1.7	84.8 ± 3.2	67.7 ± 34.1†	37.7 ± 5.8†	54.8 ± 8.1
K	30	6.9 ± .9	83.5 ± 2.7	7.8 ± 1.1	79.3 ± 2.5	4.9 ± 1.6

* Values are means ± SEM; N = 4 for each set. Abbreviations are defined in footnote to Table 1.
† Different from control values at $p < 0.05$.

30 minutes with XO ($p > 0.20$). Changes in perfusion pressure and in lung weight were uncorrelated ($r = -0.01$, $p > 0.50$).

Perfusion of the lung with HX/XO or XO alone for 10 minutes or 30 minutes resulted in significant inhibition of 5-HT removal ($p < 0.05$) and prolongation of the t½ for removal ($p > 0.05$) as compared with control values (Table 1). Perfusion for 30 minutes with HX/XO or XO as compared with 10 minutes resulted in greater inhibition of 5-HT removal and prolongation in the t½ ($p < 0.05$).

PEA removal was not significantly inhibited ($p > 0.50$) by perfusion of the lung for 10 minutes with HX/XO or XO or by perfusion of the lung for 30 minutes with XO (Table 2). However, perfusion of the lung for 30 minutes with HX/XO significantly inhibited PEA removal and prolonged the t½ of PEA removal ($p < 0.05$).

Subsequent studies documented that Krebs-Ringer solution recirculated through the rabbit lung contained unidentified reductants (K) that served as substrate for xanthine oxide to reduce ferric cyanide to ferrous cyanide (16). No attempt was made to identify these compounds.

Discussion

Biochemical defense mechanisms that destroy toxic intermediates of oxygen metabolism normally prevent oxygen toxicity. Thus, superoxide dismutase, which catalyzes the dismutation of superoxide anions to hydrogen peroxide, normally protects the cell from the "catastrophic cascade of free radical reactions" (1). However, generation of large numbers of superoxide anions in vivo during prolonged exposure to high oxygen tensions probably overwhelms natural defense mechanisms. Superoxide anions and hydroxyl radicals generated in vivo not only damage cells, but also alter the structure of DNA, depolymerize polysaccharides, cause lipid peroxidation, and auto-oxidize thiols and amines (1, 3, 5). As previously mentioned, these toxic free radicals can also be generated in vitro. Our study confirms that a model of oxygen toxicity can be achieved in the isolated perfused lung. Such a model allowed us to examine the effects of free radical-induced, severe injury on bioamine uptake and removal. Limiting the exposure of the lung to free radicals and hence limiting the degree of injury may later prove useful in testing methods for scavenging toxic free radicals (e.g., tocopherols, ascorbate, NADPH, glutathione) (1).

Vasoconstriction, not the transudation of fluid, appears to be responsible for the early, transient increase in perfusion pressure in our model. Perfusion pressure returned to normal levels as transudation of fluid to the lung become marked. This suggests that superoxide ions or hydroxyl radicals have themselves, or

initiate, vasoconstrictor effects. Indeed, we demonstrated in preliminary experiments that superoxide anions (generated in a tissue bath or in dialysis tubing) have vasoconstrictor effects on isolated segments of the pulmonary artery, intrapulmonary artery, and intrapulmonary vein (R. Altiere, D. R. Cook, unpublished observations, 1981). Iwasawa, Gillis, and Aghajanian (8) previously demonstrated that isolated lungs could be perfused for 1 hour without developing edema and without inhibition of 5-HT uptake. On the other hand, we noted in early pilot studies that lung edema in this model was greatly exacerbated if the lungs were perfused with 3% albumin solutions. For this reason, protein solutions were omitted from · our study.

The uptake of 5-HT is a temperature-, sodium-, and energy-dependent process (20, 21); 5-HT is metabolized by the A form of monoamine oxidase (9, 10). Uptake of 5-HT into the endothelial cell, rather than metabolism, is the rate-limiting step of 5-HT removal (20, 22). Monoamine oxidase A inhibitors have no effect on 5-HT removal (8, 20). Removal of PEA occurs by diffusion; 70% of PEA is deaminated by plasma monoamine oxidase and 30% of PEA is deaminated by the B form of monoamine oxidase. Metabolism of PEA is the rate-limiting step for PEA removal (9, 10, 23). In control lungs, approximately 85% of 5-HT was removed from the pulmonary circulation. We demonstrated that 5-HT removal is significantly inhibited in a dose (time)-related fashion by superoxide anions and hydroxyl radicals.

Inhibition of removal by 39% and 63% theoretically would be expected to increase the 5-HT concentrations reaching the left side of the heart of the intact animal by approximately 320% and 535%, respectively. In contrast, PEA removal was inhibited only in those lungs perfused for 30 minutes with hypoxanthine and xanthine oxide. Inhibition of monoamine oxidase activity, therefore, also can accompany severe endothelial cell injury. Acute exposure to high concentrations of ozone can injure mitochondrial and microsomal membranes and has been associated with decreased monoamine oxidase activity (1). In the case of 5-HT, inhibition of monoamine oxidase activity is pharmacologically moot because if uptake is inhibited, metabolism cannot occur. More important, there was a clear dichotomy between inhibition of PEA removal in the remaining experiments and the gross signs of endothelial damage as manifested by the increase in perfusion pressure and the development of edematous lungs. We can assume that superoxide anions or hydroxyl radicals were generated by

perfusion of the lungs with hypoxanthine and xanthine oxide for 10 minutes or by the perfusion of the lungs for 30 minutes with xanthine oxidase alone. Limited amounts of these tissue-toxic substances produce capillary leak and inhibition of an active uptake process (e.g., 5-HT removal), but not inhibition of PEA removal. PEA removal was normal despite gross edema in lungs, and this strongly suggests that there was not a large reduction of the capillary surface area of the injured lung or a loss of bioamine into the interstitial space of the lung.

The mechanism by which superoxide anions and hydroxyl radicals inhibit active uptake of 5-HT and inhibit the metabolism of PEA is unknown. Clearly, 5-HT removal was more sensitive to injury in this model than the removal of PEA. Recently, Cook and Brandom (12) noted that potent inhalation anesthetics (e.g., halothane, enflurane, and isoflurane) at equal MAC multiples also inhibited 5-HT uptake more than PEA uptake. Whether 5-HT uptake and removal is a more sensitive indicator of endothelial damage from other causes than PEA or other metabolic probes is not known. However, clinically practical techniques of determining 5-HT uptake and removal have been developed (7, 22, 24, 25). Serial measurement of 5-HT removal may be a useful clinical tool in predicting survival in various forms of adult respiratory distress syndrome.

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Enflurane, Halothane, and Isoflurane Inhibit Removal of 5-Hydroxytryptamine from the Pulmonary Circulation

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Cook, D. R., and Brandom, B. W.: Enflurane, halothane, and isoflurane inhibit removal of 5-hydroxytryptamine from the pulmonary circulation. Anesth Analg 1982;61:671-5.

We were interested in determining the effect of enflurane, halothane, and isoflurane on the uptake and removal of 5-hydroxytryptamine (5-HT) and phenylethylamine (PEA) from the lung. Isolated rabbit lungs were perfused in a recirculating system in vitro with 0.1 μM [^{14}C]5-HT or 0.1 μM [^{14}C]PEA in Krebs-Ringer solution. The rate of removal and percentage of removal of the bioamines were determined before and after either 1, 2, or 4 MAC multiples of the potent anesthetics. Because of variation in removal of bioamines among lungs from different animals, the effects of anesthetics on bioamine removal were determined by calculating the percentage of inhibition of removal using data from the control and test period for each lung. At 2 MAC concentrations, the anesthetics inhibited 5-HT removal 11.1%, at 4 MAC concentrations the anesthetics inhibited 5-HT removal 29.8% and significantly prolonged the half-life (t½) of 5-HT removal. There was significant (10.8%) inhibition of PEA removal at 4 MAC concentrations for the three anesthetics. As uptake of 5-HT is the rate-limiting step in 5-HT removal, these data demonstrate a uniform depression of 5-HT uptake by the three potent anesthetics. The rate-limiting step of PEA uptake, metabolism by monoamine oxidases, is inhibited at 4 MAC concentrations of anesthetics.

Key Words: ANESTHETICS, Volatile: enflurane, halothane, isoflurane; SEROTONIN: pulmonary uptake. LUNG: serotonin uptake.

ENDOTHELIAL cells of the lung clear certain vasoactive substances from the pulmonary circulation and activate others which then enter the systemic circulation (1). Hence, the endothelial cell may modulate both pulmonary and systemic vascular tone. Inhalation anesthetics (e.g., nitrous oxide and halothane) inhibit the removal of norepinephrine but not removal of prostaglandin E_2 from the pulmonary circulation (2, 3). Little information is available about the effects of inhalation anesthetics on the metabolism of other bioamines such as 5-hydroxytryptamine (5-HT) (4, 5).

5-Hydroxytryptamine, a potent vasoconstrictor, is actively taken up by endothelial cells of the lung, metabolized, and the metabolite released back into the pulmonary circulation (6). We were interested in determining the clearance of 5-HT and phenylethylamine (PEA), two bioamines, by the isolated perfused lung during various MAC multiples of halothane, enflurane, and isoflurane anesthesia. The uptake of 5-HT into the endothelial cell is an active process (6) whereas the uptake of PEA occurs by diffusion (7); both bioamines are metabolized by monoamine oxidases (8). Uptake of 5-HT, not metabolism, is the rate-limiting step in 5-HT removal (6). Use of these two bioamines allowed us to distinguish between the effects of potent inhalation anesthetics on active uptake by pulmonary endothelial cells and on metabolism of bioamines following uptake into endothelial cells.

Methods

Experiments were carried out using rabbit lung preparations perfused in a manner previously described by Naito and Gillis (2).

New Zealand White rabbits (2.5 to 3.0 kg) were intravenously anesthetized with thiopental (25 mg/kg) and heparinized (1000 units/rabbit); then their

hearts, lungs, and tracheas were excised en bloc from the thorax. After isolation of the main pulmonary artery, the heart was cut from the preparation, connective tissue was excised, and the trachea and each pulmonary artery cannulated; the pulmonary veins were opened to allow free drainage of effluent. The lungs were statically inflated with 20 to 25 ml of room air.

The isolated lungs were placed in a water-jacketed, humidified incubation chamber maintained at 37°C. The lungs were perfused independently but concurrently via each pulmonary artery at a constant flow rate of 10 ml/min with Krebs-Ringer bicarbonate-dextrose-hetastarch (3% w/v) solution with the following composition (mM): NaCl (118), KCl (4.75), $CaCl_2$ (2.54), KH_2PO_4 (119), $MgSO_4$ (1.10), $NaHCO_3$ (25.0), and dextrose (11.1) at 37°C. The perfusate was saturated by bubbling with 95% oxygen and 5% carbon dioxide; the pH was between 7.35 and 7.45.

Experimental Procedures

Each lung was perfused for 10 minutes with oxygenated Krebs-Ringer bicarbonate-dextrose solution to clear the lung of blood and thiopental. After this washout period, the lungs were perfused in a recirculating system from a 100-ml reservoir containing 0.1 μM [^{14}C]5-HT or 0.1 μM [^{14}C]PEA in the Krebs-Ringer solution for 15 to 16.5 minutes. [^{14}C]5-hydroxytryptamine (56 mCi/mmol), was supplied by Amersham Co., Arlington Heights, IL and [^{14}C]phenylethylamine (6.9 mCi/mmol) by New England Nuclear, Boston, MA. The reservoir was sampled at 3-minute intervals for determination of parent compound and metabolite.

The lungs were then perfused for 20 minutes with a 200-ml reservoir of dextrose-electrolyte solution that had been aerated for 30 minutes with the anesthetic gas being tested, oxygen, and carbon dioxide; aeration with anesthetic gas was continued during this period. Radioactivity from both parent and metabolite was washed from the lung for 5 minutes with the above solutions; the perfusion was then continued with a recirculating system.

Halothane, enflurane, and isoflurane at 1, 2, and 4 MAC were delivered by means of an anesthetic-specific Ohio Medical matic-type vaporizer with a flow of 3 L/min of 95% O_2 and 5% CO_2. As we did not determine the MAC of the potent agents in rabbits, we assumed the MAC of halothane to be 0.75%, the MAC of enflurane to be 1.68%, and the MAC of isoflurane to be 1.28%; those are the MAC values of

adults (human). Finally, the lungs were reperfused (recirculating system) for 15 to 16.5 minutes with new 0.1 μM 5-HT or PEA in electrolyte solution aerated with the anesthetic gas; aeration with anesthetic gas was also continued during this period. The reservoir was again sampled at 3-minute intervals for determination of parent compound and metabolite. The pH also remained stable between 7.35 and 7.45 during this period. Thus, for experimental purposes, each lung served as its own control. Four separate lungs were studied at each anesthetic concentration. Data from grossly edematous lungs were discarded.

Measurement of Amine Uptake and Metabolism

Aliquots of lung effluent (0.5 ml) were passed over columns of Biorex 70 (sodium form; pH 6.0) cation exchange resin to separate unchanged 5-HT and PEA from their deaminated metabolites, 5-hydroxyindolacetic acid and phenylacetic acid, respectively (8). Anionic and neutral products were subsequently removed from the column with 1.5 ml of glass-distilled water. The total 2.0-ml sample was then added to 4.0 ml of Aquasol liquid scintillation cocktail and the radioactivity of the solution was measured by liquid scintillation spectrometry. Radioactivity of a second 0.5-ml aliquot added to 1.5 ml of water was measured without passage over columns to determine total radioactivity. Distintegrations per minute (dpm) were calculated from appropriate quench curves. The parent compound (nmol/ml) and metabolite (nmol/ml) of bioamine was calculated at each time period. Radioactivity (dpm) associated with the parent compound is the difference between the total disintegrations per minute and the disintegrations per minute of the deaminated metabolite.

Calculation of Half-Life and Percentage of Removal

A plot of log concentrations of parent compound against time revealed a linear relationship, which suggested that first-order kinetics was applicable over the period studied (Figure) (7). The slope, K_{10}, of the plot of log dose over time was calculated from a regression analysis; therefore $Ke = K_{10}/2.303$. The half-life ($t\frac{1}{2}$, min) was calculated from the relationship $t\frac{1}{2} = 0.693/Ke$.

The percentage of removal of 5-HT and PEA was calculated at each time period with the aid of an Apple II computer using the relationship: percentage of removal (%R) = Co $-$ C_t/Co $\times$ 100 (where Co = concentration of 5-HT or PEA in reservoir at time 0, and C_t = concentration of 5-HT or PEA in reservoir
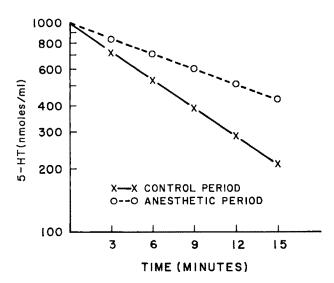
FIGURE. Relationships between concentration of 5-HT (nmol/ml) in perfusate and time of perfusion during control period and 4 MAC isoflurane anesthesia in a typical experiment. Semilogarithmic plot of 5-HT concentration vs time demonstrates linear decrease over period of study. Removal of 5-HT was inhibited 30.8% by 4 MAC isoflurane.

at time t). Bioamine removal was not corrected for sampling volumes. The maximum removal for each bioamine is presented in Tables 1 and 2.

Because of variation in removal of bioamines among lungs from different animals and between lungs of the same animal, the effects of anesthetics on bioamine removal were determined by calculating percentage of inhibition using data from the control and test period for each lung. Percentage of inhibition of removal is determined from the formula: $\%I = (Rc - Rt) \times 100/Rc$ (where Rc = percentage of removal during the control period and $Rt = Rc$ percentage of removal during the test period).

Statistical Methods

Statistical significance was evaluated by a paired t-test except in comparisons of percentages of inhibition caused by different anesthetics or different concentrations of the same anesthetic for which a one-way analysis of variance was used.

TABLE 1

Removal of 5-Hydroxytryptamine (5-HT) from Pulmonary Circulation and Its Inhibition by Anesthetics*

Anesthetic	MAC	t½		Removal		Inhibition of removal
		Control	Treated (anesthetic)	Control	Treated (anesthetic)	
		min		%		%
Halothane	1	5.3 ± 0.4	5.8 ± 1.0	86.3 ± 1.0	83.7 ± 3.0	2.9 ± 0.8
	2	7.1 ± 0.8	8.0 ± 0.8	76.8 ± 2.4	68.1 ± 1.9†	11.3 ± 1.8
	4	3.9 ± 0.9	9.8 ± 1.3	94.5 ± 3.1	65.0 ± 4.2†	31.2 ± 4.8
Isoflurane	1	4.7 ± 0.5	5.30 ± 0.5	89.4 ± 1.3	86.7 ± 1.7	3.0 ± 2.0
	2	7.0 ± 1.2	8.7 ± 1.1	77.7 ± 3.7	70.7 ± 3.9†	9.0 ± 2.5
	4	6.5 ± 1.0	12.3 ± 0.9	79.5 ± 3.2	57.5 ± 3.0†	27.7 ± 3.6
Enflurane	1	5.2 ± 0.7	5.8 ± 0.8	85.8 ± 2.7	83.2 ± 2.0	3.1 ± 1.8
	2	5.6 ± 1.3	6.2 ± 1.3	91.7 ± 3.8	80.6 ± 4.0†	12.2 ± 3.5
	4	6.2 ± 0.5	12.5 ± 1.8	80.7 ± 1.9	55.9 ± 6.0†	30.7 ± 7.1

* Values are means ± SD. Data from four lungs were used to calculate the values presented.
† Different from control values at $p < 0.05$.

TABLE 2

Removal of Phenylethylamine (PEA) from Pulmonary Circulation and Its Inhibition by Anesthetics*

Anesthetic	MAC	t½		Removal		Inhibition of removal
		Control	Treated (anesthetic)	Control	Treated (anesthetic)†	
		min		%		%
Halothane	4	8.2 ± 0.6	8.0 ± 0.7	79.4 ± 3.7	70.6 ± 1.7†	11.0 ± 3.2
Isoflurane	4	8.5 ± 0.8	8.3 ± 1.0	79.7 ± 1.8	69.7 ± 2.5†	12.5 ± 2.1
Enflurane	4	8.1 ± 0.8	7.8 ± 0.9	78.4 ± 3.9	71.3 ± 3.8†	9.1 ± 2.3

* Values are means ± SD. Data from four lungs were used to calculate the values presented.
† Different from control values at $p < 0.05$.

Results

The t½ for the rate of removal of 5-HT was significantly prolonged as compared with the control t½ at 4 MAC for each of the three anesthetics ($p < 0.05$) (Table 1).

There was no inhibition of 5-HT removal at 1 MAC concentrations of halothane, enflurane, or isoflurane ($p > 0.50$) (Table 1). There was significant inhibition of 5-HT removal at 2 and 4 MAC for each anesthetic ($p < 0.05$); the percentage of inhibition increased significantly from 2 to 4 MAC of each anesthetic ($p < 0.05$). However, there was no significant difference in the degree of inhibition of 5-HT removal among the three anesthetics at equal MAC multiples ($p > 0.20$).

There was significant inhibition of PEA removal by an average of 10.8% at 4 MAC for the three anesthetics ($p < 0.05$), but no significant difference ($p > 0.20$) between the degree of inhibition of PEA between the three anesthetics at 4 MAC (Table 2). The removal of PEA was not tested at 1 and 2 MAC for the three anesthetics.

Discussion

The active uptake process of 5-HT within pulmonary capillary endothelial cells is sodium, ATP, and energy dependent (6, 8, 9). Because the uptake of 5-HT is energy dependent, we speculated that inhalation anesthetics would inhibit 5-HT uptake at concentrations clinically used. Indeed, halothane, enflurane, and isoflurane significantly inhibited 5-HT removal approximately 11% at 2 MAC and approximately 30% at 4 MAC multiples. Byles et al (4), likewise, noted no change in arterial 5-HT concentration in dogs following approximately 1 MAC concentrations of halothane, enflurane, isoflurane, and methoxyflurane. In prior studies, Naito and Gillis (2) noted inhibition of norepinephrine removal from the lung by both halothane and nitrous oxide. Combining halothane with nitrous oxide produced additive inhibition of norepinephrine removal. At equally potent concentrations, halothane inhibits removal of norepinephrine to a greater degree than removal of 5-HT. The reason(s) for this is not clear.

The mechanism responsible for inhibition of 5-HT active uptake by pulmonary endothelial cells by higher concentrations of inhalation anesthetics is unknown. There may be enzymatic inhibition of sodium-potassium ATPase (10, 11), inhibition of aerobic metabolism necessary for 5-HT transport, or an alteration in membrane permeability. A common mechanism appears involved for all three potent anesthetics as the same degree of inhibition was seen as equal MAC multiples of anesthetics. Rannels, Watkins, and Biebuyck (5) noted inhibition of 5-HT uptake by 4% halothane in isolated rat lungs perfused in situ. In contrast to our study, halothane altered metabolism of 5-HT at high (20 μM) substrate concentrations but not at low substrate concentrations (2 μM). Differences in experimental methods may explain this dichotomy with our study (i.e., they limited the perfusion period to 2 minutes [single-pass technique], in their study lungs were perfused in situ, and the flow rate of perfusion in their study was probably greater than in our study). There was no depletion of ATP in the rat lungs nor was there a change in the extravascular space from high concentrations of halothane.

The uptake of PEA is by diffusion. The rate-limiting step of PEA uptake is related to the metabolism of PEA to phenylacetic acid (7). Seventy percent of PEA is deaminated by plasma monoamine oxidase and 30% of PEA is deaminated by the B form of monoamine oxidase. PEA removal was inhibited only 10.5% at 4 MAC concentrations of the three anesthetics. Presumably, this inhibition of metabolism of PEA is related to a reduction in aerobic metabolism with a reduction in plasma and B form monoamine oxidase activity. A comparable degree of inhibition of 5-HT removal was seen at 2 MAC concentration for the three anesthetics. This makes it unlikely that significant inhibition of PEA removal would be seen at 1 or 2 MAC concentrations of the anesthetics. For this reason, we elected not to study PEA removal at 1 and 2 MAC concentrations of the anesthetics. Inhalation anesthetics appear to depress the active transport processes for bioamine uptake into endothelial cells to a greater degree than they depress the metabolism of bioamines by monoamine oxidases. Likewise, the active transport processes for bioamines in the lung appear more susceptible to lung injury from superoxide radicals than do the metabolism of bioamines (12).

It is difficult to assess the full physiologic and clinical implications of this study. Pulmonary release of vasoactive materials or inhibition of the uptake of others is likely a major factor in the constriction of pulmonary vessels associated with hypoxic ventilation, pulmonary edema, and pulmonary embolism (13). Although prostaglandins or thromboxanes may be the mediators of hypoxic pulmonary vasoconstriction, it seems likely that 5-HT and additional vaso-

active substances such as angiotensin I and bradykinin may also participate in this response (13). Potent inhalation anesthetics, such as isoflurane and fluroxene, blunt the vasoconstrictor response to hypoxia, whereas halothane anesthesia augments the response; these changes in the hypoxic vasoconstrictor response due to potent halogenated anesthetics are minimal at 1 MAC and become more marked at 2 and 3 MAC multiples of anesthetic (14). As approximately 85% of 5-HT in pulmonary arterial blood is normally removed from the lung, we estimated that 17.6% inhibition of removal would double the 5-HT concentration entering the left heart, and that 52.9% inhibition of removal would quadruple the 5-HT concentration entering the left heart. Thus, 11% inhibition of removal of 5-HT by 2 MAC and 30% inhibition at 4 MAC by the potent anesthetics may profoundly influence both pulmonary and systemic vascular resistance. Additional data will be needed to clarify the effect of anesthetics on any complex physiologic changes such as hypoxic pulmonary vasoconstriction. Such data must include the effects of anesthetics on the removal of additional vasoactive substances from the lung (e.g., angiotension I or bradykinins).

ACKNOWLEDGMENT

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Clinical Evaluation of a New Fiberoptic Catheter Oximeter during Cardiac Surgery

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WALLER, J. L., KAPLAN, J. A., BAUMAN, D. I., AND CRAVER, J. M.: Clinical evaluation of a new fiberoptic catheter oximeter during cardiac surgery. Anesth Analg 1982;61:676–9.

A new pulmonary arterial catheter (Opticath), containing the standard pulmonary artery catheter features plus two fiberoptic filaments to permit continuous measurement of oxygen saturation ($S\bar{v}_{O_2}$) by a companion oximeter, was studied in 13 patients undergoing elective coronary bypass surgery. The study was designed to evaluate the accuracy of Opticath $S\bar{v}_{O_2}$ measurements, to determine the incidence of catheter-related problems, and to correlate changes in $S\bar{v}_{O_2}$ with hemodynamic changes. A good correlation was found between the $S\bar{v}_{O_2}$ determined by the Opticath and that measured by American Optical and Radiometer Oximeters (r = 0.92 and 0.89 respectively; p < 0.0001). There was a significant correlation between increases or decreases in values of $S\bar{v}_{O_2} \geq$ 5% and corresponding changes in cardiac index, stroke index, and left ventricular stroke work index (p < 0.001), and an 86% probability that $S\bar{v}_{O_2}$ decrease $\geq$5% reflected a significant decline in cardiac index.

Key Words: OXYGEN: measurement; MEASUREMENT TECHNIQUES: oximeter.

PULMONARY arterial catheters are now commonly used in patients undergoing cardiac surgery. The majority of catheters now in use permit continuous monitoring of pulmonary arterial and central venous pressures, but only intermittent measurements of pulmonary capillary wedge pressure and cardiac output. Presently, the determination of mixed venous oxygen tension or oxygen saturation ($S\bar{v}_{O_2}$) necessitates sending a pulmonary arterial blood sample to the laboratory. A new pulmonary arterial catheter (model P7110 Opticath, Oximetrix Inc, Mountain View, CA) contains the standard pulmonary arterial catheter features plus two fiberoptic filaments to permit continuous measurement of $S\bar{v}_{O_2}$ by a companion oximeter. Although on-line umbilical arterial oxygen saturation monitoring with this oximeter has proved useful in neonates (1), neither the P7110 Opticath nor the oximeter system has been evaluated during cardiac surgical procedures in adult patients. Therefore, this study was designed to evaluate this pulmonary arterial catheter and oximeter (the Opticath system) in such patients by: (a) correlating in vivo $S\bar{v}_{O_2}$ measurements with standard laboratory in vitro $S\bar{v}_{O_2}$ results, (b) correlating on-line $S\bar{v}_{O_2}$ changes with hemodynamic changes, and (c) determining the incidence of equipment malfunctions and catheter-related complications.

Methods and Materials

The protocol was approved by the Human Investigations Committee of Emory University, and informed consent was obtained from each patient before the catheter was inserted. Thirteen patients scheduled for elective coronary artery bypass grafting were studied. Mean age was 54 ± 7 (SD) years, and weight was 84 ± 14 kg with body surface areas of 2.0 ± 0.2 m². The patients had multivessel coronary artery disease involving 3.3 ± 1 vessels. All patients were maintained on full doses of beta-adrenergic blocking drugs and nitrate preparations until surgery. They were premedicated with diazepam, 8.8 ± 4.3 mg, orally, and morphine sulfate, 8.8 ± 2.0 mg, and scopolamine, 0.3 or 0.4 mg, intramuscularly.

When patients arrived in the operating room two

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large-bore intravenous lines, a 20-gauge radial arterial catheter, and an Opticath pulmonary arterial catheter were placed percutaneously in sequence utilizing standard aseptic technique and local infiltration with 1% lidocaine. Patients were anesthetized with diazepam, 0.4 ± 0.1 mg/kg, morphine sulfate, 1.0 ± 0.2 mg/kg, 50% nitrous oxide/oxygen, and intermittent enflurane in low inspired concentrations. The inspired oxygen concentration was kept constant between successive paired measurements, and a Perkin-Elmer mass spectrometer was used to measure end-tidal oxygen, carbon dioxide, and enflurane tensions.

Intravascular pressures, heart rate and rhythm, cardiac output (triplicate thermodilution) and derived parameters, in vivo $S\bar{v}_{O_2}$ (Opticath), two in vitro $S\bar{v}_{O_2}$ values (American Optical Unisat Oximeter and Radiometer OSM-II Hemoximeter), arterial blood gas tensions, and hematocrit were determined simultaneously at each study interval. Intravascular pressures were measured with Statham P50 transducers and all data recorded on a Gould-Brush multichannel recorder. In vivo $S\bar{v}_{O_2}$ values were recorded continuously on the strip chart recorder built into the Oximetrix instrument.

Control measurements were made while the patients were awake, and serial measurements were made following anesthetic induction and tracheal intubation, just before skin incision, following median sternotomy, during placement of cardiopulmonary bypass circuit cannulae, after discontinuation of cardiopulmonary bypass, and at any time during the procedure when in vivo $S\bar{v}_{O_2}$ values increased or decreased by 5% or more.

The Opticath was evaluated to determine the time required for insertion, the frequency of difficulties during insertion or use, and the incidence of complications. The system was evaluated throughout surgery and for 12 to 24 hours in the postoperative intensive care unit. Multiple blood samples were drawn to compare the in vitro and in vivo $S\bar{v}_{O_2}$ measurements throughout both the operative and intensive care phases of the study. Linear regression analysis was used to compare $S\bar{v}_{O_2}$ determined by the Opticath with $S\bar{v}_{O_2}$ measurements using the two in vitro oximeters, and to correlate changes in in vivo $S\bar{v}_{O_2}$ values with hemodynamic changes.

Results

The Opticath was inserted successfully in all 13 patients without the aid of fluoroscopy. The catheter felt relatively stiff in handling compared with other thermodilution pulmonary arterial catheters, presum-

ably because of its fiberoptic bundles. Less than 3 minutes was required to pass the catheter from the superior vena cava to the wedge position in 10 of the 13 patients. This sequence required 3, 5, and 10 minutes, respectively, in the three others, who were the first three patients in the series. Premature ventricular contractions were observed in six of the 13 patients. In four patients, these were frequent and multifocal and were successfully treated with intravenous lidocaine (1 mg/kg). There were no other catheter-related complications in this series. There was one equipment malfunction, and therefore, the results of only 12 patients are presented; the one patient dropped from the study was deleted due to failure of the optical module. In the remaining 12 patients, the oximeters and catheters functioned normally throughout the study and for the next 12 to 24 hours after surgery in the intensive care unit.
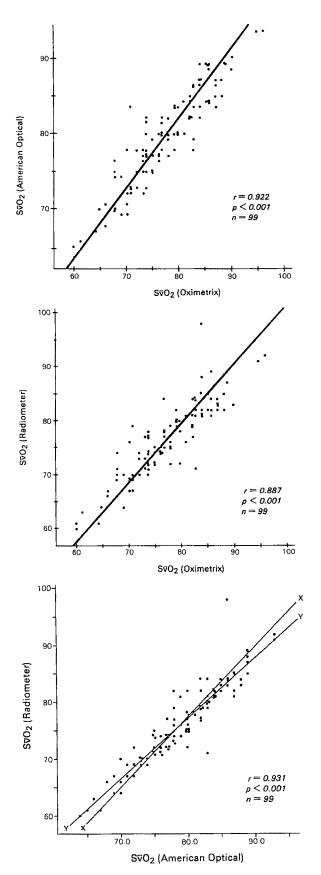
There was a good correlation between the $S\bar{v}_{O_2}$ determined by the Opticath and that measured by the American Optical ($r = 0.92$, n = 99) and Radiometer ($r = 0.89$, n = 99) oximeters (both $p < 0.001$; Fig 1, top and middle). There was also an excellent correlation between the two in vitro oximeters ($r = 0.93$, n = 99); (Fig 1, bottom). This was true for the range of $S\bar{v}_{O_2}$ values from 60% to 95%, measured with hematocrits of 20% to 42%.

Changes in $S\bar{v}_{O_2}$ values also correlated with hemodynamic changes. There was a highly significant positive correlation between increases or decreases in $S\bar{v}_{O_2}$ values $\geq 5\%$ and corresponding changes in cardiac index ($r = 0.69$; Fig 2), stroke index ($r = 0.67$), and left ventricular stroke work index ($r = 0.58$, all $p < 0.001$).

There were 39 instances during the study when $S\bar{v}_{O_2}$ values changed by 5% or more. Eighteen of the 21 (86%) decreases in $S\bar{v}_{O_2}$ were accompanied by corresponding decreases in cardiac index, and 14 of the 18 (78%) $S\bar{v}_{O_2}$ increases were also accompanied by increased cardiac index. In vivo $S\bar{v}_{O_2}$ values did not correlate with changes in mean arterial pressure, heart rate, pulmonary capillary wedge pressure, or systemic vascular resistance (Table).

Discussion

These data demonstrate that the Opticath system used during surgery provides accurate, on-line, in vivo $S\bar{v}_{O_2}$ measurements. The accuracy obtainable with this instrument is satisfactory for clinical use, and the equipment appears to be reliable. Calibration and set-up of the oximeter required less than 5 minutes.

The Oximetrix oximeter was originally used to measure in vivo arterial oxygen saturation in sick, newborn infants via a companion #4 French, 2-lumen umbilical artery catheter. Wilkinson et al (1-3) noted stable oximeter performance and a high correlation (r = 0.97) with cuvette oximeter readings when they used the instrument in the intensive care unit and during immediate postnatal resuscitation of asphyxiated infants.

The concept that cardiac output affects arterial and venous blood oxygen content is widely accepted (4-6). In 1967, Kelman et al (7) pointed out that a decrease in cardiac output in the face of constant oxygen consumption leads to an increase in oxygen extraction from the blood, and therefore, a reduction in mixed venous blood oxygen content. Therefore, $S\bar{v}_{O_2}$ values decline as cardiac output is reduced. If arterial oxygenation is maintained and oxygen consumption does not change markedly during anesthesia, changes in $S\bar{v}_{O_2}$ values should reflect changes in cardiac output.

This relatively simple physiologic relationship cannot be used clinically when $S\bar{v}_{O_2}$ values must be

$Y = 0.06853(x) - 0.13189$

$r = 0.694, \quad p < 0.001$
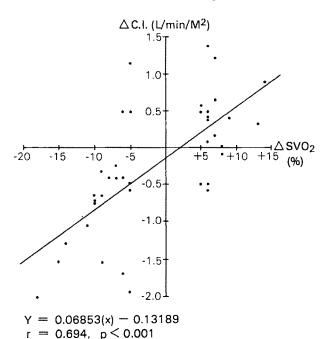
Fig 2. Correlation of on-line $S\bar{v}_{O_2}$ changes measured by Opticath with corresponding changes in cardiac index. There were 39 instances during study when $S\bar{v}_{O_2}$ values changed by 5% or more, declining 21 times and increasing 18 times. Cardiac index did not change in same direction in only seven instances.

Fig 1. Oxygen saturation as measured by three oximeters. There was good correlation between $S\bar{v}_{O_2}$ values measured by Opticath and American Optical (top) and Radiometer (middle) oximeters, as well as between Radiometer and American Optical oximeters (bottom).

TABLE

Hemodynamic Data and $S\bar{v}_{O_2}$ Changes during Cardiac Surgery*

	Increased $S\bar{v}_{O_2}$ (N = 18)		Decreased $S\bar{v}_{O_2}$ (N = 21)	
	Control	$\geq$5% $\uparrow$ $S\bar{v}_{O_2}$	Control	$\geq$5% $\downarrow$ $S\bar{v}_{O_2}$
$S\bar{v}_{O_2}$ (%)	74.7 $\pm$ 6.3	81.9 $\pm$ 6.0	79.9 $\pm$ 4.8	71.3 $\pm$ 4.2
MAP (mm Hg)	85.4 $\pm$ 14.0	86.6 $\pm$ 10.3	77.0 $\pm$ 20.6	81.6 $\pm$ 14.5
HR (beats/min)	78.8 $\pm$ 15.3	80.9 $\pm$ 8.4	78.8 $\pm$ 10	82.4 $\pm$ 25.0
$\overline{PA}$ (mm Hg)	18.8 $\pm$ 5.6	18.3 $\pm$ 4.5	15.8 $\pm$ 3.7	16.0 $\pm$ 5.1
PCWP (mm Hg)	11.1 $\pm$ 3.1	11.7 $\pm$ 3.4	9.7 $\pm$ 2.8	9.6 $\pm$ 3.1
CVP (mm Hg)	8.6 $\pm$ 2.3	8.1 $\pm$ 3.1	8.1 $\pm$ 3.1	8.1 $\pm$ 3.6
CI (L/min/m^2)	2.30 $\pm$ 0.53	2.63 $\pm$ 0.50$\dagger$	2.62 $\pm$ 0.73	1.94 $\pm$ 0.58$\dagger$
SI (ml/m^2)	30.0 $\pm$ 8.0	32.5 $\pm$ 6.6$\dagger$	33.4 $\pm$ 8.7	24.7 $\pm$ 7.2$\dagger$
LVSWI (gH/m/m^2)	30.4 $\pm$ 9.4	32.0 $\pm$ 9.4$\dagger$	32.7 $\pm$ 9.5	24.5 $\pm$ 8.7$\dagger$
SVR (dyne$\cdot$sec$\cdot$cm^{-5})	1391.5 $\pm$ 463.7	1211.3 $\pm$ 340.2	1209.9 $\pm$ 362.8	1623.9 $\pm$ 528.0
HCT (%)	30.5 $\pm$ 5.4	31.2 $\pm$ 6.1	31.8 $\pm$ 9.1	32.1 $\pm$ 6.7
Pa$_{O_2}$ (mm Hg)	243.5 $\pm$ 103.8	259.0 $\pm$ 84.7	185.4 $\pm$ 103.0	202.9 $\pm$ 983.0
Pa$_{CO_2}$ (mm Hg)	40.5 $\pm$ 5.0	41.1 $\pm$ 5.5	39.1 $\pm$ 4.7	37.4 $\pm$ 4.7
P$\bar{v}_{O_2}$ (mm Hg)	41.5 $\pm$ 6.5	45.6 $\pm$ 7.3	40.9 $\pm$ 10.2	36.7 $\pm$ 4.2

* Values are means $\pm$ SD. Abbreviations used are: $S\bar{v}_{O_2}$, mixed venous oxygen saturation; MAP, mean arterial pressure; HR, heart rate; $\overline{PA}$, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; CI, cardiac index; SI, stroke index; LVSWI, left ventricular stroke work index; SVR, systemic vascular resistance; HCT, hematocrit; Pa$_{O_2}$, arterial oxygen tension; Pa$_{CO_2}$, arterial carbon dioxide tension, P$\bar{v}_{O_2}$, mixed venous oxygen tension.

$\dagger$ Correlation with $S\bar{v}_{O_2}$ change significant, $p < 0.001$.

measured from discreet blood samples drawn from a pulmonary arterial catheter and analyzed in a remote laboratory. The Opticath, which utilizes soft plastic catheters as light guides and light-emitting diodes as light sources, updates the $S\bar{v}_{O_2}$ measurement every second. Therefore, it is possible to use $S\bar{v}_{O_2}$ determinations as an early clue to large changes in cardiac output.

In 1973, Martin et al (8) reported accurate in vivo $S\bar{v}_{O_2}$ measurements utilizing an earlier catheter oximeter system. Although these authors suggested that the changes in $S\bar{v}_{O_2}$ that they saw represented changes in cardiac output, they could not confirm this, as they did not measure cardiac output in their patients. Our study documents a highly significant correlation between changes in $S\bar{v}_{O_2}$ values and changes in cardiac output and other hemodynamic variables in cardiac surgical patients. This correlation, although statistically highly significant, is not so strong that clinically reliable quantitative inferences can be made from the $S\bar{v}_{O_2}$ changes alone. However, when $S\bar{v}_{O_2}$ values decreased by 5% or more, there was an 86% probability in our study that cardiac index had also decreased. Therefore, decreases in in vivo values of $S\bar{v}_{O_2}$ can provide an early qualitative warning of substantial hemodynamic deterioration, and guide the physician in determining when to make cardiac output measurements and alter therapy.

This study demonstrates the reliability of the Opticath system, and the strong probability that changes in $S\bar{v}_{O_2}$ represent corresponding hemodynamic changes. This system appears to have potential applications for monitoring patients with low cardiac output states or other forms of cardiac or respiratory insufficiency both in the operating room and intensive care units.

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Low-Dose Fentanyl Blunts Circulatory Responses to Tracheal Intubation

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The effect of fentanyl, 8 μg/kg, used as an adjunct to thiopental for induction of anesthesia, on the circulatory response to tracheal intubation was investigated in 36 patients undergoing major vascular surgery. Patients were randomly assigned to receive either thiopental, 6 mg/kg, alone (N = 18), or thiopental, 3 mg/kg, along with fentanyl, 8 μg/kg (N = 18), for induction of anesthesia. The electrocardiogram, arterial pressure, pulmonary capillary wedge pressure, cardiac output, and central venous pressure were measured during induction of anesthesia, laryngoscopy, and intubation. Mean arterial blood pressure increased more following intubation in patients given thiopental than in patients given fentanyl-thiopental, reaching a peak value of 144 ± 4 torr in patients receiving thiopental only, compared with 108 ± 6 torr in those receiving fentanyl and thiopental ($p < 0.0001$). Increases in systolic blood pressure, diastolic blood pressure, and pulmonary capillary wedge pressure with intubation were also significantly greater following administration of thiopental than following fentanyl-thiopental. Doses of fentanyl that are low enough to cause little postoperative respiratory depression significantly blunt postintubation hypertension when used as an adjunct to thiopental.

Key Words: INTUBATION: tracheal; ANESTHETIC TECHNIQUES: laryngoscopy; ANALGESICS: fentanyl.

LARYNGOSCOPY and tracheal intubation after induction of anesthesia with thiopental are frequently associated with severe hypertension. Increases in mean arterial pressure from 20 to 40 torr when compared with awake control levels (1–3), and 35 to 60 torr when compared with preintubation values (1–4), have commonly been reported after placement of an endotracheal tube. This postintuba-

tion hypertension is particularly severe in patients with preoperative hypertension and cardiovascular disease. Mean blood pressure increased an average of 52 torr following intubation in a series of 14 hypertensive patients undergoing aortic bifurcation grafting (5).

Lunn et al (6) have shown that an induction dose of fentanyl, 50 μg/kg, abolished the increase in blood pressure and heart rate associated with tracheal intubation in a series of patients undergoing coronary artery surgery. More recently, Bennett and Stanley (7) have observed a similar effect of as little as 4 μg/kg of fentanyl given after a 10-minute N_2O-O_2 induction in presumably normotensive general surgical patients. Neither of these groups, however, examined the effect of fentanyl during a rapid barbiturate induction. Therefore, we undertook a prospective, randomized study to determine the effect on postintubation hypertension of "low" doses of fentanyl when used as part of a thiopental-relaxant induction. The study was conducted in patients with vascular disease who, therefore, were at increased risk of postintubation hypertension.

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Methods

Thirty-six patients undergoing major vascular surgery were studied with their informed consent and the approval of the Committee on Studies involving Human Beings.

Premedication consisted of morphine, 0.1 mg/kg, and either atropine, 0.007 mg/kg, for the 20 patients undergoing carotid endarterectomy, or scopolamine, 0.007 mg/kg, for the 16 patients undergoing aortic bifurcation grafting. Before surgery, patients undergoing each procedure were randomly assigned to one of two treatment groups.

All patients first breathed 100% oxygen for 60 seconds, then received thiopental, 3 mg/kg, followed by pancuronium, 0.1 mg/kg. Then the 18 patients in group I received fentanyl, 8 μg/kg, over 2 minutes beginning 1 minute after they received thiopental. The 18 patients in group II received another dose of thiopental, 3 mg/kg, 3 minutes after their first dose and before laryngoscopy.

Laryngoscopy was begun 4 minutes after pancuronium was given, and was followed by placement of an endotracheal tube lubricated with sterile surgical lubricant containing no local anesthetic. After intubation, anesthesia was maintained with 50% N_2O in O_2 for 4 minutes, the remainder of the study period. After the study period, the anesthetics used were not controlled.

Electrocardiogram lead V_5, direct arterial pressure, and central venous pressure were measured in all patients. Pulmonary capillary wedge pressure (PCWP) and thermodilution cardiac output (in duplicate) were measured in the patients undergoing aortic bifurcation grafting. Heart rate; systolic, diastolic, and mean arterial pressures; PCWP; central venous pressure; cardiac index; stroke volume index; left ventricular stroke work index; and systemic vascular resistance were compared between group I and II patients at four time periods: (a) awake and unstimulated, (b) 30

to 90 seconds before intubation at the time when blood pressure was lowest, (c) 30 to 90 seconds after intubation at the time when blood pressure was highest, and (d) 4 minutes after intubation when the hemodynamics had stabilized.

Hypotension was defined as a mean blood pressure less than 80% of a patient's preoperative mean blood pressure or 75 torr, whichever was lower. Ephedrine, 5 mg IV, was used to treat hypotension of this degree. Hypertension was defined as a mean blood pressure greater than 120% of a patient's preoperative mean blood pressure, or 120 torr, whichever was higher. Trimethaphan, given intravenously in 1-mg increments, was used to treat hypertension. The incidence of hypotension and hypertension requiring treatment was recorded and compared between treatment groups.

The incidence of arrhythmias after intubation was compared between groups. An arrhythmia was defined as any ventricular or supraventricular premature beat or any sustained rhythm other than sinus. Arrhythmias were considered related to intubation if they appeared for the first time or increased in frequency by at least 4 beats per minute in the 2 minutes following intubation. Data were initially examined using multivariate analysis. Where variance was found, either Student's t-test, for parametric data, or the chi-square test, for nonparametric data, was used to determine the significance of differences between the two treatment groups, with $p < 0.05$ considered statistically significant.

Results

Patients in the two groups did not differ significantly in weight, preoperative blood pressure or pulse, the incidence of preoperative propranolol therapy, or the incidence of a diagnosis of hypertension, angina, or congestive heart failure in their medical records. The duration of laryngoscopy was similar in both patient groups (Table 1). The mean age of the patients

TABLE 1

Patient Characteristics*
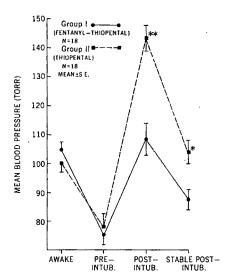
	Age†	Weight†	Mean BP†	Pulse†	PCWP‡	Patients with history of hypertension†	Duration of laryngoscopy†
	yr	kg	torr	beats/min	torr		sec
Group I (fentanyl-thiopental)	68.3 ± 1.5	67.7 ± 2.3	105 ± 2.6	74.8 ± 3.1	13.1 ± 1.2	10	27 ± 10
Group II (thiopental only)	63.2 ± 1.4§	74.2 ± 2.4	100 ± 2.9	82.7 ± 3.6	10.1 ± 0.9	12	29 ± 8

* Values are means ± SEM. Abbreviations used are: BP, blood pressure; PCWP, pulmonary capillary wedge pressure.
† N = 18 for groups I and II.
‡ N = 8 for groups I and group II.
§ $p < 0.05$.
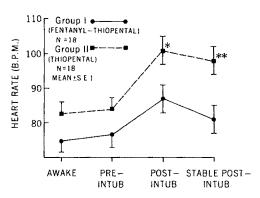
FIG 1. Mean arterial pressure during induction of anesthesia and tracheal intubation in patients receiving both thiopental and fentanyl (group I) or thiopental only (group II).

FIG 2. Heart rate during induction of anesthesia and tracheal intubation.

FIG 3. Pulmonary capillary wedge pressure (PCWP) during induction of anesthesia and tracheal intubation. Absolute values of PCWP did not differ significantly between treatment groups at any time.

given fentanyl-thiopental was 68 years compared with 63 years in those given thiopental.

With induction of anesthesia, mean blood pressure decreased to a similar extent in both groups (Fig 1). The number of patients receiving ephedrine and the doses of ephedrine used were similar in both patient groups. Seven patients given fentanyl-thiopental and four patients given thiopental alone required ephedrine to treat hypotension before intubation ($p > 0.2$). Patients receiving thiopental only, however, reacted to intubation significantly differently than those intubated following administration of fentanyl and thiopental. Mean blood pressure increased to 108 ± 6 torr after fentanyl-thiopental, 3 torr above awake control and significantly ($p < 0.0001$) lower than the value of 144 ± 4 torr found in patients given thiopental. Fifteen patients given thiopental received trimethaphan to treat postintubation hypertension, an average dose of 4.3 ± 1.5 mg/patient. Three of the patients receiving thiopental and fentanyl required trimethaphan, an average dose of 0.4 ± 0.3 mg/patient ($p < 0.05$).

Heart rate increased slightly with induction of anesthesia and administration of pancuronium in both groups (Fig 2). Following intubation, the absolute value of the heart rate was significantly greater after thiopental than after fentanyl-thiopental ($p < 0.05$). The increase in heart rate with tracheal intubation, however, was not significantly different between the two groups.

PCWP increased with laryngoscopy and intubation after thiopental from an awake value of 10 ± 1 torr to

18 ± 2 torr. After fentanyl-thiopental, however, postintubation PCWP did not exceed the awake value of 13 ± 2 torr (Fig 3). The increase in the PCWP with intubation was significantly ($p < 0.05$) greater in patients given thiopental than in those given fentanyl-thiopental (Fig 4).

Differences between the two groups in cardiac index, stroke volume index, left ventricular stroke work index, systemic vascular resistance, and central venous pressure did not reach statistical significance (Table 2). Further, there were no statistically significant differences in any hemodynamic variables between those patients, within each treatment group, who did or did not have a preoperative history of hypertension.

Three of the patients given thiopental and one of those given fentanyl-thiopental had arrhythmias related to intubation. None of the arrhythmias required

treatment. Chest wall rigidity was not noted following fentanyl-thiopental. All patients given fentanyl-thiopental were extubated in the operating room and did not require reintubation. The highest postoperative P_{CO_2} value in any patient was 47 torr. No anesthetic complication was observed in either group of patients.

Discussion

Postintubation pressor responses have been asso-
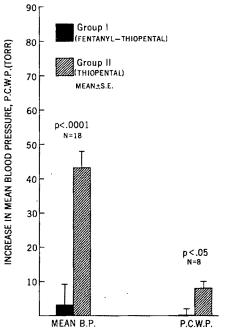
FIG 4. Elevation of the mean arterial pressure and PCWP following tracheal intubation, compared with preinduction levels, plotted for patients in both treatment groups.

ciated with ST segment changes (4), ventricular arrhythmias (4), pulmonary edema (8), and rupture of cerebral aneurysms (8). Some authors, in fact, consider the intubation period one of the periods of greatest risk in surgical patients with coronary artery disease (9).

Various methods to attenuate the sympathetic response to laryngoscopy have been studied. King et al (10) found that deep ether anesthesia abolished the response, but in a more recent study in hypertensive patients Prys-Roberts et al (4) found that the pressor response was not completely blocked by 1% halothane given for 5 to 10 minutes and occurred with all the induction agents studied.

Topical anesthesia of the pharynx along with superior laryngeal nerve blocks reduced the increase in mean arterial pressure after intubation from approximately 45 to 22 torr in one series (11), whereas intratracheal lidocaine spray caused a 50% reduction in this hypertensive response in a more recent series of cardiac patients (12). Stoelting (3), further, found that intravenous lidocaine alone, or the combination of viscous lidocaine and topical intratracheal lidocaine, was more effective in blunting the hypertensive response than intratracheal lidocaine alone, especially if laryngoscopy required more than 15 seconds (1). Most recently, Stoelting (2) effectively used a bolus of nitroprusside to limit the increase in mean blood pressure after intubation to 13 to 18 torr when compared with awake control values. However, this technique did not block the development of tachycardia.

This study demonstrates a statistically significant reduction in postintubation hypertension, tachycardia, and PCWP elevation when fentanyl, 8 μg/kg, is

TABLE 2

Hemodynamic Changes with Intubation*

	Treatment group	Awake control	Before intubation	Immediate post-intubation	Stable post-intubation
Cardiac index (L/min/m²)	F†	3.0 ± 0.1	2.3 ± 0.2	2.7 ± 0.2	2.5 ± 0.3
	T‡	3.0 ± 0.2	2.6 ± 0.1	3.1 ± 0.2	3.0 ± 0.2
Stroke volume index (ml/m²/beat)	F†	42 ± 3	31 ± 3	32 ± 2	33 ± 2
	T‡	37 ± 1	33 ± 2	33 ± 2	32 ± 2
Left ventricular stroke work index (g· meter/m²)	F†	53 ± 5	29 ± 5	43 ± 4	37 ± 3
	T‡	49 ± 3	37 ± 4	54 ± 5	46 ± 4
Systemic vascular resistance (dynes· sec/cm⁵)	F†	1484 ± 86	1378 ± 118	1737 ± 150	1529 ± 96
	T‡	1396 ± 124	1286 ± 79	1776 ± 77	1429 ± 125
Central venous pressure (torr)	F§	7.1 ± 0.7	7.9 ± 0.8	8.1 ± 0.9	6.6 ± 0.8
	T‖	7.1 ± 0.6	7.7 ± 0.6	7.6 ± 0.8	6.1 ± 0.9

* Values are means ± SEM. There were no significant differences between treatment groups in any variable.
† Fentanyl-thiopental group, N = 8.
‡ Thiopental group, N = 8.
§ Fentanyl-thiopental group, N = 18.
‖ Thiopental group, N = 18.

ued as an adjunct to a thiopental induction in patients with vascular disease. The use of fentanyl provides an alternative to intravenous lidocaine, topical lidocaine, deep inhalation anesthesia, or intravenous sodium nitroprusside, when it is necessary to blunt the cardiovascular responses to tracheal intubation in these patients.

Narcotics may block afferent nerve impulses resulting from stimulation of the pharynx and larynx during intubation. Atweh and Kuhar (13) have found, using autoradiographic techniques in the rat, high concentrations of opiate receptors in the solitary nuclei and the nuclei of the 9th and 10th cranial nerves, associated with the visceral afferent fibers of these nerves which originate in the pharynx and larynx. Further, vagal motor nuclei involved in monosynaptic pharyngeal and laryngeal motor reflexes also have a high concentration of opiate receptors. These receptors provide a possible mechanism for the antitussive effects of narcotics, as well as the blunting of the response to laryngeal stimulation we observed in this study.

Mean arterial pressure decreased with induction of anesthesia in both groups of patients in the present study. The magnitude of this decrease was dose dependent, and, indeed, relative doses of thiopental and fentanyl were chosen that resulted in similar degrees of cardiovascular depression in each treatment group (Fig 1).

It has been established that, in a general patient population, preoperative untreated hypertension, especially associated with a preoperative diastolic blood pressure greater than 110 torr, can lead to labile intraoperative blood pressure (4). In our more limited patient population consisting entirely of patients with vascular disease, however, no significant association was found between the hemodynamic responses to induction of anesthesia or tracheal intubation and either a preoperative history of hypertension or the preoperative blood pressure. It could be that all our patients, regardless of their preoperative history, had

vascular changes characteristic of hypertension, and responded to anesthesia accordingy.

We conclude that the use of fentanyl as an adjunct to a thiopental-relaxant induction is a rapid, effective, practical way to protect patients with cardiovascular disease from the stress otherwise associated with tracheal intubation.

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Cardiovascular Effects of Ketamine following Administration of Aminophylline in Dogs

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STIRT, J. A., BERGER, J. M., ROE, S. D., RICKER, S. M., AND SULLIVAN, S. F.: Cardiovascular effects of ketamine following administration of aminophylline in dogs. Anesth Analg 1982;61:685-8.

The induction of halothane anesthesia following intravenous administration of aminophylline may cause ventricular arrhythmias. Ketamine has been recommended for anesthesia induction and maintenance in patients with asthma. This study was designed to determine whether induction and maintenance of ketamine anesthesia following intravenous aminophylline is arrhythmogenic in dogs. One group of six dogs was anesthetized with intravenous ketamine, 5 mg/kg, followed by infusion of 5 mg/kg/hr. Three additional groups of six dogs were given intravenous aminophylline, 10, 25, and 50 mg/kg, respectively, followed 3 minutes later by intravenous ketamine, 5 mg/kg, and a 5 mg/kg/hr ketamine infusion. No arrhythmias occurred at any time in any animal. Ketamine use following aminophylline would appear to lack arrhythmogenic potential and may be advantageous in the clinical setting.

Key Words: PHARMACOLOGY: aminophylline; ANESTHETICS, Intravenous: ketamine.

KETAMINE decreases airway resistance in asthmatic patients (1) and has been recommended for use as an anesthetic in patients with bronchospasm (2). A recent study (3) concluded that "ketamine may be the agent of choice for induction of anesthesia in asthmatic patients . . . ."

Aminophylline, a mainstay in the treatment of patients with asthma and bronchospasm, is often administered before or during anesthesia induction in such patients. Anesthesia induction following aminophylline administration has been associated with ventricular arrhythmias in animals (4) and man (5, 6), and increased arrhythmogenicity following ketamine has been described (7).

As there have been no reports of the combined actions of aminophylline and ketamine, we performed this study to determine the cardiovascular effects of ketamine anesthesia induction following administration of aminophylline.

Methods and Materials

The University of California, Los Angeles Medical Center's guide for the care and use of laboratory animals was followed.

The experiment consisted of four parts. Six different dogs (a total of 24) were used in each of the four parts.

Part 1 (Control)

Six mongrel dogs (average weight 21 kg) were given thiopental, 20 mg/kg IV, followed by succinylcholine, 1 mg/kg IV. Tracheal intubation was performed immediately with a cuffed orotracheal tube, an airtight seal was produced, and the animals were ventilated with a Harvard animal respirator delivering air at 12 breaths per minute. Tidal volume was adjusted to produce an end-tidal CO_2 of 4.5% as measured by an on-line gas mass spectrometer (Perkin-Elmer MGA-1000). No further changes in respirator settings were made during the study. A lead II electrocardiogram was attached and recorded throughout the study.

A femoral arterial catheter was placed and attached to a pressure transducer (Bentley Trantec), and systolic, diastolic, and mean arterial pressures were recorded throughout the study. Heart rate was measured from the blood pressure tracing. A peripheral

venous catheter was inserted and 0.9% NaCl infused at 100 ml/hr.

When these preparations had been completed, between 10 and 15 minutes after beginning controlled ventilation, an arterial blood sample was drawn from the femoral artery for analysis of oxygen (Po_2) and carbon dioxide (Pco_2) tensions and serum pH. Three minutes later, a second control arterial blood sample was obtained and analyzed for blood gas tensions and pH.

One minute after the second blood sample, ketamine, 5 mg/kg IV, was administered over 30 seconds, and a 5 mg/kg/hr ketamine infusion was begun. Arterial blood samples were obtained 2, 5, 10, 15, and 30 minutes after ketamine was begun, and analyzed for O_2 and CO_2 tensions and pH.

Part 2

The same protocol was followed as in part 1, except that 1 minute following the initial blood sample, aminophylline (theophylline ethylenediamine, Invenex), 10 mg/kg, was infused intravenously over 1 minute. The second blood sample was obtained 1 minute after completion of aminophylline administration and analyzed as described above, with serum theophylline levels determined in duplicate by homogenous enzyme immunoassay (EMIT, Syva, Palo Alto, CA), in which competitive protein binding was determined spectrophotometrically using a labeled enzyme and specific binding antibody (8). The remainder of the protocol was as in part 1, with serum theophylline concentrations being determined in all subsequent samples.

Part 3

The same protocol was followed as in part 2, except that the aminophylline dose was 25 mg/kg.

Part 4

The same protocol was followed as in part 2, except that the aminophylline dose was 50 mg/kg.

Values reported are means ± SE; Student's t-test was used to determine the significance of differences from control values before aminophylline administration.

Results

No arrhythmias occurred in any animal at any time in any of the four parts. Peak serum theophylline levels in each animal are shown in Table 1. There were no significant differences between groups of

animals in any of the four parts in initial heart rate or blood pressure.

Heart rate increased significantly following aminophylline administration at each dose level (Table 2). In the control animals, heart rate increased following administration of ketamine, the increase becoming significant 15 minutes after ketamine was begun. In the animals in parts 2, 3, and 4, heart rate remained elevated significantly following ketamine.

Mean arterial blood pressure decreased significantly following administration of aminophylline, 50 mg/kg (Table 3). Blood pressure increased significantly in control animals 10 minutes following administration of ketamine, and increased significantly 2 minutes following ketamine in the group given 10 mg/kg of aminophylline. Blood pressure gradually increased after ketamine in the groups given 25 and 50 mg/kg of aminophylline, returning to control levels after 25 mg/kg at 30 minutes after ketamine administration.

In the control group, mean arterial blood gas tensions before ketamine were: Po_2 87 ± 3.8 torr, Pco_2 35.0 ± 0.7 torr, and pH 7.38 ± 0.02. No significant

TABLE 1

Peak Serum Theophylline Level (mg/L) in Each Animal 1 Minute following Aminophylline Infusion

Animal no.	Aminophylline		
	10 mg/kg	25 mg/kg	50 mg/kg
1	26	59	68
2	18	74	68
3	26	51	106
4	24	47	102
5	32	41	148
6	26	54	150

TABLE 2

Heart Rate (beats/min) before and after Ketamine Anesthesia following Administration of Aminophylline*

Measure-ment	Control	Aminophylline		
		10 mg/kg	25 mg/kg	50 mg/kg
1	168 ± 10	170 ± 14	170 ± 8	170 ± 10
2	166 ± 10	214 ± 18	236 ± 11†	236 ± 11†
3	176 ± 11	236 ± 17†	246 ± 8†	248 ± 4†
4	180 ± 11	228 ± 19†	234 ± 7†	246 ± 5†
5	157 ± 32	226 ± 16†	230 ± 7†	246 ± 5†
6	198 ± 9†	232 ± 9†	224 ± 8†	248 ± 5†
7	208 ± 8†	238 ± 2†	204 ± 13†	224 ± 11†

* Values are means ± SE. In control animals, measurements 1 and 2 were made 4 and 1 minutes, respectively, before ketamine administration, and 3 to 7 were obtained 2, 5, 10, 15, and 30 minutes, respectively, after beginning ketamine. In animals receiving aminophylline, measurement 1 was made 1 minute before aminophylline administration, 2 was obtained 1 minute following aminophylline (1 minute before ketamine), and 3 to 7 as in the control animals. No arrhythmias occurred in any animal at any time.
† $p \leq 0.05$.

TABLE 3

Mean Arterial Blood Pressure (torr) before and after Ketamine Anesthesia following Administration of Aminophylline*

Measurement	Control	Aminophylline		
		10 mg/kg	25 mg/kg	50 mg/kg
1	112 ± 6	113 ± 6	108 ± 6	127 ± 8
2	117 ± 6	114 ± 6	86 ± 8	64 ± 9†
3	115 ± 4	130 ± 4†	94 ± 3	83 ± 7†
4	118 ± 4	128 ± 6	85 ± 16	95 ± 7†
5	128 ± 3†	130 ± 8	103 ± 4	100 ± 8†
6	136 ± 3†	144 ± 6†	106 ± 4	105 ± 8
7	143 ± 3†	149 ± 6†	108 ± 4	111 ± 12

* Values are means ± SE. In the control animals, measurements 1 and 2 were made 4 and 1 minute, respectively, before ketamine administration and 3 to 7 were obtained 2, 5, 10, 15, and 30 minutes, respectively, after beginning ketamine. In animals receiving aminophylline, measurement 1 was made 1 minute before aminophylline administration, 2 was made 1 minute following aminophylline (1 minute before ketamine), and 3 to 7 as in the control animals.

† $p \leq 0.05$.

change occurred following ketamine administration. Mean arterial blood gas tensions 2 minutes after beginning ketamine induction in the 18 animals given aminophylline were: P_{O_2} 85.1 ± 2.6 torr, P_{CO_2} 33.8 ± 0.5 torr, and pH 7.40 ± 0.01. No significant differences from control values were noted.

Discussion

In this study, induction of ketamine anesthesia shortly after aminophylline administration did not produce cardiac arrhythmias. Aminophylline doses were identical with those found to be arrhythmogenic when followed by halothane anesthesia induction in a previous study (4). Successively larger doses of aminophylline were given, which resulted in serum theophylline concentrations considered therapeutic (approximately 10 to 20 mg/L) and arrhythmogenic (>20 mg/L) in conscious man (9).

Heart rate following the combination of aminophylline and ketamine increased significantly from control values and remained elevated for the duration of the studies. Aminophylline alone has been reported to increase heart rate in animals anesthetized with halothane (10, 11), and ketamine has also been shown to increase heart rate (12). Thus, cardioacceleration would be expected to result following the combination of aminophylline and ketamine. No arrhythmias occurred, however, although the average heart rate following aminophylline and ketamine was 243 beats per minute, similar to an average of 244 beats per

minute at the time ventricular arrhythmias occurred in animals anesthetized with halothane following aminophylline administration (4).

In both the present and an earlier study (13), the magnitude of the decrease in blood pressure after aminophylline, 25 mg/kg and 50 mg/kg, was proportional to the dose of aminophylline. In this study the decrease was statistically significant following aminophylline, 50 mg/kg.

Arterial P_{O_2}, P_{CO_2}, and pH following ketamine alone (control group), as well as after aminophylline and ketamine, were not significantly different from control values, implying that during controlled ventilation, arterial oxygenation is unaffected by either ketamine alone or the combination of ketamine and aminophylline. However, ketamine has been shown to cause arterial hypoxemia when respiration is spontaneous (14), and oxygen supplementation should probably be provided when ketamine is used during spontaneous ventilation.

Aminophylline stimulates the synthesis and release of catecholamines (15, 16), and may also act by increasing intracellular cyclic adenosine 5'-monophosphate (cAMP) (17). Catecholamines also increase cAMP (18). Ketamine has been shown to increase plasma catecholamine levels in man (19), and it causes release of catecholamines from peripheral tissue depots in both animals (20) and man (2). The bronchodilating effect of ketamine has been attributed to increased plasma levels of endogenous catecholamines (2). A cocaine-like effect of ketamine, preventing re-uptake of catecholamines, has also been reported (21, 22).

Increased circulating levels of catecholamines after ketamine administration might be expected to potentiate the effects of aminophylline and result in cardiac arrhythmogenicity. Indeed, ketamine enhances the arrhythmogenicity of epinephrine (7), although this was determined in a study in which 1% halothane and 60% nitrous oxide were administered throughout the experimental procedure. Several other investigators (23-25) have reported the opposite result, namely, that ketamine appears to have antiarrhythmic effects. Our results are consistent with the latter reports which demonstrate an antiarrhythmic effect of ketamine.

Ketamine is seldom used as the sole anesthetic, often being administered in conjunction with N_2O. Previous work in dogs (24) has demonstrated a pressor effect of ketamine, 5 mg/kg, when given during 66% N_2O in O_2. The magnitude of blood pressure elevation in that study (24) was similar to that seen in the control group in our experiments. Whether amino-

phylline and ketamine would prove arrhythmogenic during N_2O anesthesia cannot be definitively shown from our study, but we would predict that the addition of N_2O would not alter substantially the findings we report above.

In summary, a previous study (4) showed that halothane anesthesia induction following intravenous administration of aminophylline caused ventricular arrhythmias in 33% of the animals studied, even with serum theophylline levels considered therapeutic and not arrhythmogenic in conscious man. In contrast, the results of this study indicate that the induction and maintenance of ketamine anesthesia following intravenous administration of 10, 25, or 50 mg/kg of aminophylline does not cause cardiac arrhythmias in dogs. Ketamine use following aminophylline appears to lack arrhythmogenic potential and may be advantageous in the clinical setting.

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Coaxial Catheter for Humidification during Jet Ventilation

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RAMANATHAN, S., ARISMENDY, J., GANDHI, S., CHALON, J., TURNDORF, H.: Coaxial catheter for humidification during jet ventilation. Anesth Analg 1982;61:689-92.

A coaxial jet ventilation catheter capable of entraining liquid water by Venturi effect was assembled by inserting an epidural catheter (water injector tube) into a 69-cm-long, 3-mm-i.d., outer jet delivery tube. Gas jet flow in the outer tube produced a negative pressure in the inner injector tube. The entrainment pressure could be varied by increasing or decreasing the distance between the injector and jet portals. The quantity of entrained water could thus be regulated between 8 ± 1 to 44 ± 2 mg/L of gas by decreasing this distance from 3.5 to 0.5 cm. The catheter was used to deliver low- or high-frequency jet ventilation for 4 hours in dogs (five dogs per mode of ventilation) and for 2 hours in patients (12 patients per mode). Patients receiving either mode of ventilation were divided into two equal groups. One group was ventilated with dry gases and the other with humidified gases containing 44 mg H_2O/L. Ciliated epithelial cells were obtained by bronchial lavage at the onset and termination of each study. Damage to ciliated cells was assessed numerically by a point scoring system. The coaxial catheter produced adequate pulmonary ventilation both in dogs and humans during both modes of ventilation. The human tracheobronchial cellular score decreased approximately 21% after unhumidified low- and high-frequency ventilation. However, the score did not change significantly in patients who received humidified gases, indicating efficient humidification by the coaxial catheter.

Key Words: HUMIDIFICATION: jet ventilation; VENTILATION: jet, humidification.

BOTH HIGH- AND LOW-frequency jet ventilation (LFJV and HFJV) are used during anesthesia for endolaryngeal surgery (1, 2), correction of bronchopleural fistulae (3), and tracheal stenosis repair (4). High gas flows make humidification of the jet difficult. Although humidifiers have been described for jet ventilation (5), none has yet been described for catheter jet ventilation. A coaxial jet ventilation catheter, easily assembled from commonly available equipment, is described. The catheter can entrain liquid water by Venturi effect during both LFJV and HFJV.

Methods

The coaxial jet ventilation catheter (Fig 1) was

assembled. A 69-cm-long (i.d. = 3 mm, o.d. = 4 mm), plastic tube (a segment of straight type blood recipient set, Fenwal Laboratories, Deerfield, IL) served as the jet delivery tube (JT). The length and inside diameter of the tube were determined experimentally so that at clinically used tidal volumes, the jet ventilation catheter would deliver satisfactory inspired humidity. The distal end of the tube bore indelible markings 0.5 cm from the tip (point 1) and subsequently at 1-cm intervals (points 2 to 4). A disposable plastic dual injection Y-piece (McGaw Laboratories, Inc., Sabana Grande, PR) was inserted at the proximal end. The fenestrated end of a Portex epidural catheter (Portex Inc., Wilmington, MA) was cut off. The modified catheter (EC-1) with a single terminal hole was threaded through one of the rubber stoppers (RS) of the Y-piece into the outer tube until its tip reached point 1. The remaining rubber stopper of the Y-piece was left intact. The epidural catheter served as the water entrainment tube (injector tube). Preliminary tests showed that entrainment pressure and, therefore, the quantity of entrained water, could be varied by altering the distance between the tips of the injector
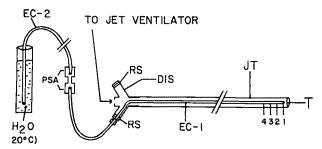
Fig 1. Diagram of coaxial jet ventilation catheter. EC-1 and EC-2 are Portex epidural catheters. (Patient ends of both catheters have been cut off at 1.5 cm from the tip.) Abbreviations used are: JT, jet delivery tube; DIS, disposable plastic dual injection site; RS, rubber stopper; PSA, Portex syringe adapter; T, patient end of the jet delivery tube. Points 1, 2, 3, and 4, which are indelible markings on jet tube, facilitate positioning of injector tip. T to point 1 = 0.5 cm and thereafter each point is 1 cm from preceding point.

and the jet delivery tube. This distance was read on the markings made on the outer jet tube (points 1 to 4). A second epidural catheter (EC-2) was used to connect the first to a water-filled burette.

Ventilation (6) was performed with a Bird Mark II ventilator, triggering a Bird parallel inspiratory flow cartridge at a driving pressure of 90 psi (F_{IO_2} = 1). The flow cartridge was connected to the jet delivery tube by a 60-cm-long, 2-mm-i.d. tube. For LFJV, a tidal volume of 500 ml at 12 breaths per minute was used with a jet pulse duration of 1 second. Corresponding figures for HFJV were 95 ml at a rate of 104 breaths per minute with each jet pulse lasting 0.12 second. The ventilatory settings (tidal volume, respiratory rate, and jet pulse duration) used during both modes of ventilation have been shown to produce adequate pulmonary ventilation (6, 7). All ventilatory parameters were measured on a lung model by pneumotachography.

Pulmonary gas exchange and humidification were assessed in experimental animals and patients during LFJV or HFJV through the catheter. In the animal study, 10 dogs (mean body weight 29 ± 2 kg) were studied. Anesthesia was induced with pentobarbital (30 mg/kg). Muscle relaxation was maintained by intermittent doses of parcuronium bromide. An indwelling femoral arterial catheter and a thermistor-tipped pulmonary arterial catheter were inserted. The dogs were divided into two equal groups.

In the first group, the coaxial catheter was inserted 4 cm below the vocal cords. Tracheal pressure was monitored 6 cm below the vocal cords using a fluid-filled catheter connected to a transducer. Dogs were ventilated by LFJV mode for 4 hours. Arterial blood pH, gas tensions, and rectal temperature were meas-

ured hourly. In the beginning of the experiment, the injector tip was at point 1 of the outer tube. The burette end of the second epidural catheter (EC-2, Fig 1) was 4 cm below water surface and approximately at the same horizontal level as the injector opening. A transducer (connected to a polygraph) was used to measure entrainment pressure at the burette end of the second epidural catheter. The quantity of entrained water was assessed by measuring change in burette water level after 1 hour. The humidity content of the jet (mg H_2O/L) was derived by dividing weight of water entrained per minute by the ventilatory minute volume. The tip of the inner epidural catheter was withdrawn to points 2, 3, and 4 at the start of the 2nd, 3rd, and 4th hour, respectively, and entrainment pressure and inspired humidity measured as above. At the end of each study, the injector opening was placed successively at 4 and 4.5 cm from the tip of the jet delivery tube and entrainment pressure measured. The outer jet delivery tube remained in situ throughout the experiment. The same protocol was used in the second group but HFJV was used. Inspired humidity and entrainment pressure during LFJV and HFJV were plotted against the distance between injector and jet portals on semilog graph paper. Mathematical equations were fitted to the curves using the curve-fitting program of the Texas Instruments-59 calculator.

The protocol for the clinical study was approved by the Committee on Human Experimentation of the New York University Medical Center. All patients gave informed consent for the procedure. Twenty-four patients who were free from cardiac or respiratory disease were studied. Mean body weight was 76 ± 9 kg and age 38 ± 6 years. All were scheduled to undergo prolonged superficial plastic surgery of the extremities. Preoperative medication included atropine, 0.4 mg, and meperidine, 75 mg IM, 1 hour before surgery. A radial artery blood sample was obtained before the start of anesthesia. Following an intravenous thiopental induction (4 mg/kg), muscle paralysis was achieved by 100 mg of succinycholine. Anesthesia was maintained with continuous infusions of 0.1% methohexital and succinycholine. The jet ventilation catheter was introduced under direct vision 4 cm below the vocal cords. A suction catheter (#18) was introduced 6 cm below the vocal cords to obtain tracheal secretions for exfoliative cytology.

Twelve patients received LFJV and the other 12 HFJV at the same ventilatory settings as in the dog study. Patients receiving either mode of ventilation were divided into two equal groups. In one group

(n = 6), the inspired gases were humidified by entraining water. The tip of the injector tube was at point 1. The second group was ventilated with dry gases. At the onset of each study, 5 ml of normal saline was instilled into the trachea through the suction catheter and tracheal secretions collected 3 minutes later by suction. Cytology smears were prepared and stained by the method of Chalon et al (8). Integrity of tracheobronchial epithelium was assessed by a point scoring system (8), one point being given for each of the following factors: (a) presence of normal cilia, (b) presence of end plate, (c) normal cytoplasmic color, (d) normal cytomorphologic features, (e) normal nuclear size, and (f) normal nuclear texture. Thus, each cell could score 0 to 6 points. As 200 cells were examined in each group of slides obtained from the same tracheobronchial washing, the total score per specimen could range from 0 to 1200 points. At the end of 2 hours of jet ventilation, tracheal smears and blood gas measurements were repeated. The jet ventilation catheter was then removed and endotracheal anesthesia administered for the rest of the procedure. Chest roentgenograms were obtained in all patients on the second post-operative day. Statistical analysis was performed by the Student's t-test. Values of $p <$ 0.05 were considered statistically significant.

Results

In dogs and humans the jet ventilation catheter produced acceptable arterial blood pH and gas tensions during LFJV and HFJV (Table). Dog temperature remained unchanged during 4 hours of experimentation in both groups of dogs. Peak intratracheal pressures were 8 ± 1 torr during LFJV and 3.8 ± 0.8 during HFJV. The catheter delivered an inspired humidity of 44 mg H_2O/L at an entrainment pressure of −220 ± 2 torr during LFJV when the injector tip was at point 1. Corresponding HFJV figures were 45 ± 3 and −23 ± 2. Entrainment pressure and inspired humidity decreased exponentially when the tip of the

inner epidural catheter was withdrawn to points 2, 3, and 4 (Fig. 2). Entrainment pressure and inspired humidity could be predicted mathematically: (a) entrainment negative pressure (torr) = 277 × $e^{-0.493 \times D}$ during LFJV and 24 × $e^{-0.23 \times D}$ during HFJV, when the distance (D) between injector and jet portals was 0.5 to 3.5 cm, and (b) inspired humidity (mg H_2O/L) = 62 × $e^{-0.58 \times D}$ during LFJV, and 61.8 × $e^{-0.596 \times D}$ during HFJV, where e is natural log. Correlation coefficient (r) was 0.98 in all instances. Entrainment pressure was zero when the injector opening was at 4 cm from the jet exit point during both LFJV and HFJV. At 4.5 cm, it was positive 6C ± 3 torr during LFJV and positive 5 ± 3 torr during HFJV.

In patients who received dry gases during LFJV,
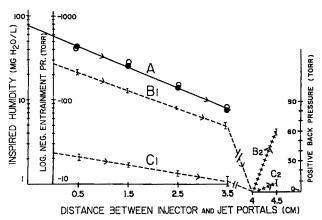
FIG 2. Inspired humidity, entrainment negative pressure, and positive back pressure as function of distance between injector and jet portals. Ordinates on left (inspired humidity and entrainment negative pressure) are logarithmic and on right (positive back pressure) arithmetic. All measurements are means of five observations. Line A, inspired humidity; open circles, LFJV; solid circles, HFJV; circle center, mean; circle diameter, ±1 SD. Entrainment negative pressure and positive back pressure were measured at burette end of second epidural catheter. Line B1, entrainment negative pressure during LFJV; line B2, entrainment negative pressure during HFJV. When distance between injector and jet portals was 4 cm, entrainment pressure was zero. When distance exceeded 4 cm, back pressure developed. Line B2, positive back pressure during LFJV; line C2, positive back pressure during HFJV.

TABLE

Arterial pH and Blood Gas Tensions after 4 Hours of LFJV or HFJV in Dogs, and after 2 Hours in Patients (F_{IO_2} = 1)*

	Dog study (n = 5)†		Human study (n = 12)‡			
	LFJV	HFJV	Control	LFJV	Control	HFJV
pH	7.55 ± 0.01	7.49 ± 0.01	7.40 ± 0.02	7.46 ± 0.03	7.39 ± 0.04	7.40 ± 0.02
Pa_{O_2} (torr)	462 ± 20	458 ± 20	96 ± 8	432 ± 28	96 ± 7	429 ± 30
Pa_{CO_2} (torr)	28 ± 3	34 ± 4	40 ± 6	33 ± 5	43 ± 6	37 ± 7

* Values are means ± SD.
† Values obtained after 1, 2, or 3 hours in the dog study were similar to those shown after 4 hours.
‡ Control measurements were made in patients while breathing room air.

mean tracheal cellular score was 920 ± 60 at the onset of ventilation. The score decreased to 728 ± 80 after 2 hours. The cellular score of patients who received unhumidified HFJV decreased from 960 ± 45 to 754 ± 88. The decrease was statistically significant in both cases ($p < 0.01$). After 2 hours of humidified LFJV, the score decreased from 912 ± 20 to 900 ± 22. During humidified HFJV, the score decreased from 904 ± 12 to 890 ± 24. The decrease was not statistically significant in both instances. Postoperative chest roentgenograms were normal in all patients.

Discussion

Our results show that the coaxial jet ventilation catheter produces adequate pulmonary gas exchange during LFJV or HFJV. There was no evidence of airway flooding (such as increased airway secretions) in either dogs or patients. No patient developed any postoperative pulmonary complication.

Pressure exerted by the gas jet is reduced during its passage through the narrow delivery tube (Bernoulli effect [9]). This pressure is restored when the jet enters a dilated passage, namely the trachea (Venturi effect [9]). Thus, a negative pressure is produced around the injector opening, causing water entrainment. The lumen of the outer tube between the injector and jet openings acted as a storage space where the entrained water collected. The jet nebulized the water and propelled it into the trachea as a fine mist. When the injector opening was at point 1 of the outer tube, the Venturi effect was maximum. Moving the tip of the inner epidural catheter to points 2, 3, or 4 increased the distance between the injector opening and the point at which the jet pressure was restored. This reduced the Venturi effect and the quantity of entrained water. Thus, humidity could be regulated by changing the distance between the injector and jet portals (0.5 to 3.5 cm). When the distance was 4 cm, the entrainment pressure was zero and at 4.5 cm, pressure was +60 torr (Fig 2). Thus, the injector portal should never be withdrawn more than 4 cm from the tracheal end of the outer tube. Withdrawal beyond this point will not only stop entrainment, but produce a back pressure in closed humidifiers.

An inspired humidity of at least 12 mg H_2O/L is required to prevent damage to tracheal epithelium (8). An inspired humidity level of 44 mg H_2O/L (saturated at 37°C) will not only prevent tracheal epithelial damage, but respiratory heat loss as well (8). In our study, the tracheal cellular score diminished by approximately 21%, (indicating some damage to tracheal

epithelium) in patients who were ventilated with dry gases for 2 hours during both LFJV and HFJV. When the gases were humidified, the cellular score did not change significantly, indicating adequate humidification by the coaxial catheter. The inspired humidity delivered by our catheter will be 8 mg H_2O/L when the injector opening is at 3.5 cm from the jet portal. When the distance between the two openings is 0.5 cm, the catheter will deliver 44 mg H_2O/L. The catheter can be made to deliver any desired inspired humidity level by simply positioning the injector opening at the appropriate distance from the jet delivery point. Anesthesiologists can use either the mathematical formulas described under "Results" or Fig 2 to determine this distance. Although HFJV produced an entrainment negative pressure approximately 9 times smaller than LFJV, both modes entrained approximately the same volume of water. This was because HFJV rate was approximately 9 times faster.

Humidifier systems have been described for jet ventilation through endotracheal tubes (5) in which humidity is derived from two sources: (a) humidified circuit oxygen entrained by the jet, and (b) small drops of saline delivered in front of the nozzle by an infusion pump generating a pressure of 18 psi. On the contrary, to use our catheter, endotracheal intubation is not required. As jet force creates an entrainment pressure, additional equipment is unnecessary. The subambient pressure found at the injector outlet prevents back pressure in the humidifier.

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technical COMMUNICATION

Extrathoracic Cuff Pressure Reflects Changes of Intrathoracic Large Airway Circumference

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The pressure measured in water-filled cuffs of endotracheal tubes has been used to evaluate the effect of drugs and physiologic stimuli on large airway tone. In six mongrel dogs, extrathoracic cuff pressure was monitored while simultaneously monitoring intrathoracic tracheal circumference measured by an implanted mercury strain gauge. The airways of each animal were alternately dilated with intravenous aminophylline (10 mg/kg) and constricted with edrophonium (10 mg). In each animal a significant linear relationship was found between cuff pressure and intrathoracic tracheal circumference. The slopes of these linear relationships were consistent for each animal, but varied between animals. In a second group of 11 dogs, cuff pressure was measured at extrathoracic and intrathoracic tracheal sites, as well as in the left main stem bronchus. Similar directional changes in cuff pressure were found at each site. This suggests that a water-filled system monitoring cuff pressure in the extrathoracic trachea reflects the direction of circumference change in the intrathoracic trachea and major bronchi.

Key Words: EQUIPMENT: cuffs, endotracheal; LUNG: bronchi.

The measurement of tracheal cuff pressure using a water-filled cuff of an endotracheal tube positioned

in the extrathoracic airway has been used in both animal and human studies to evaluate the effects of physiologic stimuli and pharmacologic agents on airway smooth muscle tone (1–5). Water is used to fill the cuff because it is incompressible and provides a reliable coupling device between tracheal wall and transducer (Fig 1). The implication of these studies (1–5) is that cuff pressure changes are representative of changing airway smooth muscle tone throughout the intrathoracic airways. However, this has never been demonstrated.

This study provides evidence that extrathoracic cuff pressure changes are indeed a reliable measure of simultaneous changes in intrathoracic large airway circumference.

We have used the mercury strain gauge (MSG) technique described by Scarpelli et al (6) to measure intrathoracic tracheal circumference and have compared these MSG measurements with cuff pressure changes recorded simultaneously during acute drug-induced changes in tracheal circumference.

Also, using a Carlen's double-lumen tube, we have shown that changes in left main stem bronchial cuff pressure parallel changes in extrathoracic cuff pressure. This is further evidence that changes in extrathoracic cuff pressure may represent changes occurring in the large intrathoracic airways.

Methods and Materials

The cuff of the endotracheal tube in each study was flushed with water, ensuring that no air remained in the cuff or tubing. The tubing from the cuff was then attached to a pressure transducer (Statham P23Db) positioned at the same height as the cuff (Fig 1). The pressure in the cuff system was continuously recorded using a Beckman Dynograph.

We studied two types of endotracheal cuff: (a) a Shiley, low-pressure, high-volume polyvinylchloride cuff placed in the extrathoracic trachea; and (b) the latex, low-volume, high-pressure cuffs of a Carlen's double-lumen tube, placed in the intrathoracic trachea and left main stem bronchus.
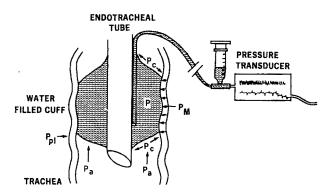
FIG 1. Factors determining pressure (P) within water-filled cuffs used in this study. P_a, Airway pressure; P_M, pressure resulting from tracheal muscle tone; P_{pl}, pleural pressure (for intrathoracic cuffs); and P_c, compliance characteristics of cuff material.

We studied 17 dogs. Anesthesia was induced with intravenous pentobarbital, 30 mg/kg, and maintained with additional 50-mg doses as necessary. A femoral arterial cannula was inserted to sample blood for blood gas analysis, and blood pressure was continuously recorded on the Beckman Dynograph.

Group A

Six of the dogs were intubated with a Shiley endotracheal tube. The cuff was then filled with water until, during ventilation, no air leak was noted around the cuff and an extrathoracic cuff pressure (P_{Te}) of 30 to 35 torr was obtained. A thoracotomy (median sternotomy) was performed and a MSG was positioned around the trachea and sutured to the intercartilagenous surface of the intrathoracic trachea. The MSG is a mercury-filled, silicone rubber tube (0.3 mm i.d., 0.63 mm o.d.), driven by a constant source of current, in which resistance changes directly and linearly with changes in length (6). While the chest was open ventilation was maintained with an Ohio 560 ventilator. The thoracotomy was then closed, air was vented from the thoracic cavity, and spontaneous respiration resumed.

In these six dogs, we were thus able to record simultaneously tracheal circumference, as measured by the implanted intrathoracic MSG, and P_{Te}.

Group B

In 11 dogs a Carlen's double-lumen tube was inserted through a tracheostomy such that both cuffs were within the thorax. The positions of both the left bronchial cuff and the intrathoracic tracheal cuff were checked using the underwater seal technique of Sykes et al (7), and verified after each experiment through dissection of the trachea. In all 11 dogs, intrathoracic

cuff pressures of the trachea (P_{Ti}) and left main stem bronchus (P_{Bi}) were recorded using the Carlen's tube.

In six of these 11 dogs, a standard esophageal balloon was inserted to monitor pleural pressure (P_{pl}). In the remaining five dogs we measured P_{Te} using the cuff of a Shiley tube positioned above the tracheostomy stoma.

All measurements reported in this study were made with dogs breathing spontaneously and with supplemental oxygen given to prevent hypoxemia.

In every experiment, at least 15 minutes was allowed to establish steady base line values before altering the resting smooth muscle tone by drug administration. We were able to induce sudden changes in tone through alternate intravenous administration of edrophonium (10 mg) and aminophylline (10 mg/ kg), given at 30-minute intervals. Alternating drugs that constrict and dilate the airways over a 2-hour period allowed us to evaluate the consistency of the
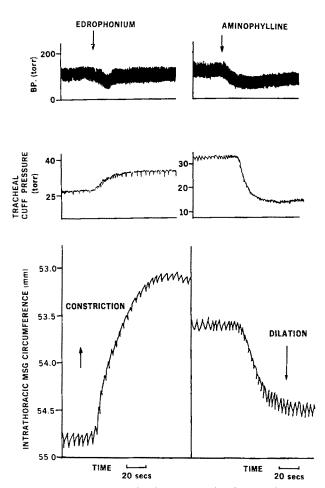
FIG 2. Traces from one dog in group A showing simultaneous changes in blood pressure (BP), extrathoracic cuff pressure (P_{Te}), and intrathoracic tracheal circumference (MSG) during tracheal constriction and dilation.

relationship between changes in cuff pressures and, in group A, changes in intrathoracic tracheal circumference as measured by the MSG.

All values quoted are means ± SD. Regression lines were computed using the method of least squares.

Results

Group A: P~Te~ and MSG Measured Circumference

The volume of water in the extrathoracic cuffs found necessary to seal with the tracheal wall and ensure a P_{Te} of 30 torr was 8.10 ± 0.56 ml.

In each experiment a change of intrathoracic tracheal circumference (MSG) was accompanied by an appropriate directional shift in P_{Te}. These changes (Fig 2) were simultaneous and were noted to be time related to the drug-induced hypotension.

To evaluate the relationship between the change in P_{Te} and the intrathoracic tracheal circumference change, we plotted values of P_{Te} and MSG circumference taken at 10-second intervals after drug administration until the peak change in MSG measured circumference occurred (Fig 3). In these six animals there were 18 drug administrations (nine aminophylline, nine edrophonium). When the data points were connected for each acute change in airway circumference (Fig 3), the relationships approximated a linear regression. Linear regression analysis was performed on each acute change in airway circumference. The

slope of these regression lines ranged from −2.22 to −88.1. However, in individual dogs, there was no significant difference between the slopes of these regression lines when aminophylline was given as compared with edrophonium ($p > 0.1$). For each acute change in airway circumference, the slope of the regression line was negative, indicating that in all cases, when the intrathoracic trachea dilated, extrathoracic cuff pressure decreased, and when the intrathoracic trachea constricted, P_{Te} increased (Fig 3).

A consistent relationship between P_{Te} and MSG measured circumference was not found when different animals were compared. Thus, similar changes of intrathoracic tracheal circumference were associated with markedly different changes of P_{Te} (Fig 3).

In two of the six experiments, mechanical problems with the implanted MSG precluded complete data collection.

Group B: P~Te~ and Intrathoracic Cuff Pressure

The responses to intravenous aminophylline and edrophonium were time related with each other and also with the hemodynamic changes (Fig 4). In six of these animals the response to drug administration was reflected by changes in P_{Ti} (cuff volume 4.73 ± 0.45 ml). When peak changes in P_{Ti} were plotted against changes in the P_{Te}, a significant linear relationship was found (Fig 5). A significant linear relationship was also found in the 11 animals when the changes in P_{Ti} were compared with the changes in P_{Bi}
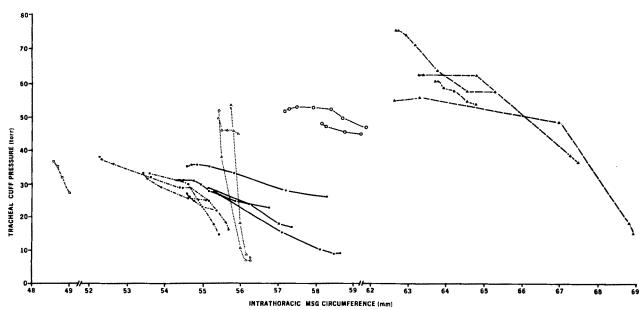
FIG 3. Simultaneous measurements of extrathoracic tracheal cuff pressure (P~Te~) and intrathoracic tracheal circumference (MSG) in six dogs in group A. Data from each dog are repre-sented by different symbols. Points joined are taken at 10-second intervals during each acute drug-induced change in tracheal circumference.

(cuff volume 2.73 ± 0.31 ml) ($r = 0.82$, $n = 55$, $p < 0.01$). In all dogs, each time a drug was administered, P_{Te}, P_{Ti}, and P_{Bi} responded in the same direction. No significant change in P_{pl} was noted indicating that changes of P_{Ti} and P_{Bi} were not secondary to changes
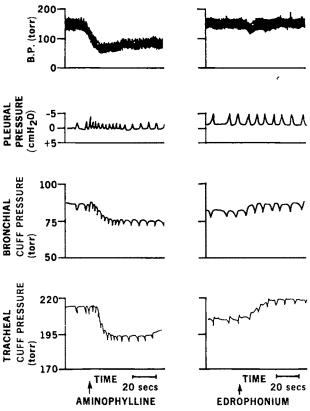
Fig 4. Traces from one dog in group B showing pleural pressure (P_{pl}), intrathoracic tracheal (P_{Ti}) and bronchial (P_{Bi}) cuff pressures, as well as simultaneous changes in blood pressure.
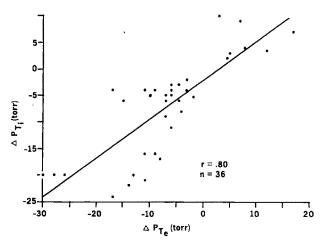
Fig 5. Peak changes of extrathoracic cuff pressure (ΔP_{Te}) are compared with simultaneous changes in intrathoracic cuff pressure (ΔP_{Ti}) in dogs in group B after aminophylline and edrophonium administration.

of surrounding pleural pressure, which could alter intrathoracic cuff pressure (Fig 1).

Discussion

The major conclusion of this study is that directional changes in extrathoracic cuff pressure accurately reflect similar directional changes of intrathoracic airway circumference. At least with the pharmacologic agents used, these changes in cuff pressure reflected changes in the large airways, both intrathoracic and extrathoracic. Hence, the basic uncertainty as to whether measurements of extrathoracic tracheal cuff pressure reflect a localized phenomenon is removed.

Fleisch and Calkins (8) have speculated that some pharmacologic stimuli influence the large and small airways independently. Our study was not an attempt to investigate the uniformity of this pharmacologic response to drugs. Therefore, we chose aminophylline, which has been shown to relax the bronchus as well as the trachea of mammalian airways (9), and edrophonium, which constricts large airways in dogs (9). Whether smaller bronchi and bronchioles constrict and dilate in a similar pattern in response to these agents remains conjectural.

Himori and Taira (5) have used the water-filled cuff of an endotracheal tube to demonstrate dose-dependent responses of the tracheal musculature to acetylcholine and various adrenergic drugs. This implies that quantitative changes in large airway tone are reflected by changes in the measured cuff pressure. Our data suggest that the direction of this response is correct, and in any individual animal the magnitude of extrathoracic cuff pressure change bears a linear relationship with intrathoracic circumference (Fig 3).

The pressure in a water-filled cuff (P) of an endotracheal tube (Fig 1) is a function of various surrounding influences. The absolute value of P is directly related to the volume of water in the cuff, the compliance of the cuff material (P_c), as well as tracheal smooth muscle tone (P_m). Changes in P caused by altered smooth muscle tone may be attenuated by the stress-relaxation properties of the cuff material exposed to the airway (not apposed to the tracheal wall). McGuiness et al (10) have discussed the physical factors that determine the pressure within an air-inflated cuff. These authors, in explaining asymmetric inflation tendencies, have shown that the diameter and thickness of thin-walled cylinders of rubber and plastic can vary. If the stress in any portion of the cuff wall exceeds the capacity of the material to withstand

stress, that portion will balloon out and cuff pressure (P) will decrease in spite of the increase in cuff volume. If this occurs in "isovolumic" water-filled cuffs, then a true decrease in tracheal circumference might cause ballooning in a thin portion of the cuff exposed to airway pressure (Pa) (Fig 1), with a resultant decrease in P.

We found that P_{Te} always changed in the appropriate direction in response to dilating and constricting influences (Fig 3). The physical properties of the polyvinylchloride cuff did not cause cuff pressure to decrease when airway constriction occurred within the range of cuff pressures studied. The range of changes of P_{Te} was similar to that found in other studies (2, 3).

In dogs in group A, the relationship between P_{Te} and MSG remained stable throughout the 2- to 2½-hour study period (Fig 3), suggesting that the elastic properties of the cuff material remain relatively constant during this time frame.

If stress-relaxation of the cuff material were to occur to a variable degree in each cuff, the change in P_{Te} for a given change in MSG-measured circumference would be variable. Thus, one explanation for the difference in slopes of this relationship (Fig 3) may relate to the properties of the cuff material.

One limitation of the technique must be related to the volume of the water in the cuff. If the trachea dilates to the point that the area of contact between the tracheal wall and the cuff is reduced to a critical value, P_{Te} will decrease toward atmospheric pressure independently of airway circumference. This critical value is probably different for various cuff materials. In our study, the phasic respiratory fluctuations of P_{Te} were always maintained during measured changes in airway tone, indicating constant contact between cuff and tracheal wall.

The tracheal circumferences in the extrathoracic and intrathoracic sites were not equal. As the cuff itself distorts the extrathoracic trachea and, at least theoretically, produces an isovolumic segment of trachea, it was impossible to measure airway circumference at the same level as P_{Te}. The particular measurement sites chosen could account for the difference in the slopes of the regression lines between animals (Fig 3). The finding that each animal had a consistent relationship between P_{Te} and MSG-measured circumference is also compatible with this explanation.

A true difference in the responsiveness of the different segments of airway studied (8) could also account for some of the variability in slopes found between animals (Fig 3).

Each MSG was calibrated before being implanted, and throughout each study the MSG detected fluctuations in airway circumference with respiration. Thus, we believe the MSG technique sensitively and accurately measured tracheal circumference at the intrathoracic site.

Croteau and Cook (11) have studied the volume-pressure relationship of isolated human tracheal and bronchial segments obtained at autopsy. With increasing age, there was a progressive decline in airway compliance. This airway compliance variable may limit the ability of cuff pressure measurements to be compared between animals at the same cuff volumes. This factor, however, would not alter the relationship between changes in airway circumference and changes in P_{Te}. Whether airways were stiff or compliant in a given dog, any change in circumference would be detected by cuff pressure changes and MSG measurement changes.

In Fig 5 is shown that in dogs in group B, simultaneous measurements of the peak change in P with each cuff are closely related in spite of the different types of cuff material and cuff locations within the trachea. This emphasizes that the high resting pressure within a latex cuff is largely due to the compliance of the cuff material, but that this higher resting pressure does not prevent the sensitive detection of small pressure changes due to altered airway tone (1, 4). The continuous traces of the hemodynamic response (BP), the MSG measurement of circumferences, and the various cuff pressures in both groups A and B (Figs 2 and 4) demonstrate that each type of cuff can respond rapidly to changes in airway circumference.

Examining the continuous recordings of P_{Ti} and P_{Bi} (Fig 4) measured with latex cuffs, we consistently noted smaller changes in P_{Bi} than in P_{Ti} after drug administration. In every case, however, the direction and timing of the response of P_{Bi} were similar to those of P_{Ti}. This difference in cuff pressure response may have been due to a difference in the length of the cuff exposed to the bronchial wall, to a reduced responsiveness of the bronchus, or to a difference in the compliance characteristics of the two cuffs.

The five animals in which pleural pressure was measured in group B (Fig 4) demonstrated that the cuff pressure did not result from changes in pleural pressure. There can be no doubt from the work of Sullivan et al (1, 4) and our experiments that changes of pleural pressure would be reflected by similar directional changes in P_{Ti} or P_{Bi}, as these cuffs are in the thoracic cavity (Fig 1). Thus, extrathoracic cuff

pressure reflects changes in the intrathoracic large airway circumference (Fig 3) and is independent of pleural pressure and hence lung volume. Our data also suggest that the changes in extrathoracic cuff pressure reported by Sullivan et al (1, 4) probably reflected extensive alterations in tracheobronchial tone throughout the large airways during sleep.

All techniques presently used to assess airway tone in patients are nonspecific (12) for the site of airway obstruction. Ingram and McFadden (12) have speculated that specific therapy for large or small airway constriction must await sensitive methods of detecting changes in tone in specific segments of the tracheobronchial tree. The continuous recording of tone using cuff pressure permits the investigator to evaluate changes relative in time to other events. The other static measurements such as resistance, specific conductance, and flow-volume curves do not have this advantage as they are measured at one point in time. As well, the airway resistance measurements vary inversely with lung volume (13).

The study of bronchomotor reflexes requires methods that can detect changes in airway dimensions both sensitively and accurately. The measurement of P_{Te} enabled us to detect quantitatively small changes in tracheal circumference. The pharmacologic agents used to induce these acute changes have previously been shown to dilate and to constrict airway smooth muscle. During these acute changes, P_{Te} accurately reflected the direction of airway circumference change to the level of the main bronchi. However, some caution must be exercised in interpreting the quantitative assessment of cuff pressure changes between individuals, as we found markedly different changes of P_{Te} for a similar magnitude of intrathoracic tracheal circumference change. In individual animals, how-ever, the size of P_{Te} change was closely related to the change in intrathoracic tracheal circumference.

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Acute Pulmonary Edema during Laparoscopy

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Laparoscopy is a frequently performed gynecologic procedure. Despite the stress of insufflation of several liters of carbon dioxide or nitrous oxide and extreme Trendelenburg position, few cardiorespiratory anesthetic complications have been reported. Unexplained cardiovascular collapse resulting in death in clinically healthy patients during laparoscopy is an extremely rare but tragic occurrence. A case of acute fulminant pulmonary edema shortly after insufflation for laparoscopy in a young patient without known cardiopulmonary disease is described in this report.

Case Report

The patient, a 27-year-old woman, was scheduled to undergo diagnostic laparoscopy to identify disease processes that could result in infertility. She had been in excellent health, with no history of cardiopulmonary disease. Preoperative laboratory values were: hemoglobin, 12.9 g%; hematocrit, 38.3%; white blood count, 3000/mm³; serum potassium, 4.1 meq/L; blood urea nitrogen, 11 mg/100 ml. Her preoperative chest roentgenogram was clear and the

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electrocardiogram unremarkable. She had general anesthetics on two previous occasions without complications.

Preoperative medications were 10 mg of morphine and 0.2 mg of glycopyrrolate intramuscularly, 2 hours earlier. Before induction of anesthesia, she was given a total of 75 µg of fentanyl, and to block fasciculations, 20 mg of gallamine. She was preoxygenated for 3 minutes before administration of 250 mg of thiopental followed by 100 mg of succinylcholine. She was ventilated with 100% oxygen, and 4% lidocaine was sprayed into the larynx and trachea. A tracheal tube was easily inserted and both lungs were ventilated easily. The patient was given 70% nitrous oxide in 30% oxygen and surgery began. Carbon dioxide insufflation of the peritoneal cavity was started. Shortly after the onset of insufflation (approximately 1 to 2 minutes), the heart rate increased from 90 to 150 beats per minute (sinus tachycardia) and the systolic blood pressure decreased to 80 torr. The patient was given 100% oxygen and within 1 minute copious amounts of pink frothy secretions were noted in the tracheal tube. The insufflation was terminated immediately. A diagnosis of acute pulmonary edema was made. The patient was given 5 cm H_2O positive end-expiratory pressure (PEEP), intravenous fluids, and a phenylephrine infusion to maintain blood pressure. She began to awaken in less than 5 minutes, and incremental intravenous injections of diazepam to a total dose of 25 mg were administered for sedation. Laboratory values at this time were: Pa_{O_2}, 59 torr; Pa_{CO_2}, 49 torr; pH 7.22; base excess, −9 meq/L; and hemoglobin, 15.9 g%. Metabolic acidosis was treated with 88 meq of sodium bicarbonate intravenously. Over the next 60 minutes, vasopressor therapy (intravenous phenylephrine infusion), continuous positive pressure ventilation, and intravenous furosemide resulted in the following arterial blood gas values: Pa_{O_2}, 209 torr; Pa_{CO_2}, 46 torr; pH 7.39; and base excess, −2 meq/L. A diagnostic peritoneal lavage with saline was performed under local anesthesia and did not reveal free blood in the peritoneal cavity. Within 90 minutes of the onset of difficulties, the patient's condition had stabilized and she was transferred to the intensive care unit without vasopressor support. She extubated herself 4 hours later. Reintubation was not necessary. A chest roentgenogram taken on arrival in the intensive care unit showed a picture consistent with low-pressure pulmonary edema and a small cardiac silhouette. Intraoperative hypotension was aggravated by hypovolemia caused

by the acute shift of intravascular fluid into the lungs as reflected by the increase in hemoglobin concentration from 12.8 to 15.9 g% and the favorable response to subsequent fluid administration, Trendelenburg position, and alpha-adrenergic vasopressors. An electrocardiogram in the intensive care unit was unremarkable. Her pulmonary edema resolved entirely within 8 hours and she was subsequently discharged on the second postoperative day and did not return for a repeat procedure.

Discussion

Although extremely rare, unexplained cardiovascular collapse resulting in death in clinically healthy patients during laparoscopy has occurred (1, 2). Carbon dioxide embolism during laparoscopy has been reported previously (3). Without the intensive and vigorous therapy that was administered immediately, this case could easily have progressed to a less favorable outcome. This frightening case emphasizes that an acute cardiovascular catastophe can occur during laparoscopy.

In this case, the more common causes of pulmonary edema (i.e., preexisting heart disease, anesthetic overdose, arrhythmias, increased blood pressure, tachycardia, hypoxia, negative airway pressure, and fluid overload) can be eliminated. Extreme Trendelenburg position and elevated central venous pressure have been described as causing acute pulmonary edema (4), but our patient was not in an extreme head-down position during the intraperitoneal insufflation. Idiosyncratic drug reactions were unlikely to be the cause of pulmonary edema in our patient: the only drugs that the patient had not already received previously were morphine, glycopyrrolate, lidocaine, and gallamine. Glycopyrrolate, lidocaine, and gallamine have not been reported as causing pulmonary edema. Narcotics can precipitate pulmonary edema in certain situations (5-8). However, it is unlikely that this patient developed pulmonary edema 2 hours after receiving 10 mg of morphine intramuscularly. She had received fentanyl during a previous anesthetic without problems.

The onset of pulmonary edema shortly after the onset of insufflation with carbon dioxide leads us to the conclusion that the most likely cause for the patient's acute pulmonary edema was introduction of carbon dioxide into the vascular system and a resultant gas embolus. Venous air embolism is known to cause acute pulmonary edema in animal experiments and has been reported clinically in humans (9, 10).

Unfortunately, an esophageal stethoscope was not utilized and the opportunity to hear the murmur of gas emboli was missed. The negative peritoneal lavage documented that there was no significant amount of free blood in the peritoneal cavity, but does not eliminate the possibility of intravascular insufflation. The diagnosis of pulmonary edema secondary to CO_2 embolism under clinical circumstances often is a diagnosis by exclusion. Venous carbon dioxide would be excreted by the lungs quickly and, therefore, confirmatory tests cannot be made after several hours. A capnograph would have reflected an increased alveolar P_{CO_2}, but this monitor is not used routinely in most institutions. Wadwha et al (11) attempted to detect gas embolism during laparoscopy in 100 cases and concluded that Doppler ultrasonic monitoring was not necessary for this procedure. Bruhl (12) reviewed 63,845 laparoscopies for diagnostic procedures other than tubal ligation and found only one case of gas embolism among 1594 serious complications. Although unintended intravascular insufflation of carbon dioxide during laparoscopy occurs rarely, it can lead to precipitous cardiovascular collapse and pulmonary edema that requires immediate and vigorous therapy.

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Anesthesia, Catecholamines, and Hemodynamics in Autonomic Dysfunction

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The anesthetic management of patients with autonomic dysfunction associated with orthostatic hypotension has been described in only three case reports (1–3). Cardiovascular instability is characteristic in autonomic dysfunction (4). We present here the first report of hemodynamic monitoring with pulmonary arterial catheterization before, during, and after anesthesia administered to a patient with orthostatic hypotension caused by autonomic dysfunction. In addition, we present, for the first time, measurements of plasma levels of catecholamines obtained perioperatively and intraoperatively from such a patient.

Case Report

A 50-year-old, 50-kg white woman was admitted to the hospital in February 1981, for emergency repair of a pathologically fractured right femur.

The patient was known to have had orthostatic hypotension of 1 year's duration caused by autonomic dysfunction, which itself probably occurred as a complication of disseminated breast carcinoma. Marked orthostatic hypotension had developed in February 1980, and was characterized at that time by a decrease in blood pressure from 114/84 torr (supine) to an unrecordable level while sitting (the patient became dizzy on sitting).

An extensive search for a specific cause for her malady was unrevealing. In March 1980, a series of pharmacologic

studies was performed to define the nature of her autonomic insufficiency with the following results: (a) the patient's response to exogenous alpha and beta agonists (phenylephrine and isoproterenol) was abnormally brisk, (b) plasma catecholamine levels (radioenzymatic assay) in the supine position were markedly depressed, and (c) lymphocyte beta-receptor density was more than twice normal. These findings were consistent with autonomic neuropathy accompanied by denervation hypersensitivity.

The patient was treated with a regimen of d-amphetamine, propranolol, fludrocortisone, sodium chloride, elastic stockings, and head-up body tilt at night, and was ambulatory on discharge in March 1980, with a supine blood pressure of 120/80 torr and an asymptomatic standing pressure of 78/50 torr.

She was readmitted to the hospital in May 1980, with progressive lower extremity motor and sensory deficits. A left-sided Horner's syndrome was present, as was autonomic colon dysfunction. Following a myelogram, which revealed block of the thoracic spinal canal from T1-11, a decompression laminectomy was performed.

The patient returned to the hospital, as noted above, in February 1981. In addition to the femoral fracture, a left-sided hearing loss of 1 month's duration was noted, as well as a new left VIIth cranial nerve palsy. A history of occasional seizures during the 6 months preceding this admission was obtained. Previous hospital and anesthesia records could not be located at the time of the planned reduction of the fracture, and it was decided that, in view of the patient's history of severe orthostatic hypotension and the urgent nature of the procedure which precluded an extensive evaluation, invasive hemodynamic monitoring was indicated for optimal preoperative, intraoperative, and postoperative management.

Premedication consisted of morphine, 8 mg, and hydroxyzine, 75 mg IM. Fentanyl, 110 µg, was used for sedation during insertion of radial and pulmonary arterial catheters, during which time the patient remained comfortable and calm. Anesthesia was induced with thiopental, 200 mg IV, with tracheal intubation after pancuronium, 6 mg IV. Following induction, an additional 150 µg of intravenous fentanyl, 60% N_2O in O_2, and 4 mg of intravenous pancuronium along with controlled ventilation were used for anesthesia during the 2-hour open reduction and intramedullary rodding of the fracture. The only cardiovascularly active drug used during the anesthesia was 33 µg of phenylephrine, which was administered intravenously 7 minutes before incision as a test dose over 3 minutes. Blood pressure before administration was 96/52 torr. Blood pressure responded briskly, increasing to 150/80 torr, following which phenylephrine was discontinued.

At the completion of surgery, residual neuromuscular blockade was antagonized with pyridostigmine, 10 mg IV, and glycopyrrolate, 0.05 mg IV, and the patient was awake and extubated immediately following the procedure. She
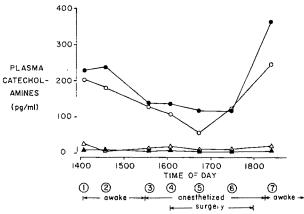
stated that she was comfortable, and she required no additional medication during the 90 minutes immediately following completion of surgery.

Blood loss for the procedure totaled 1200 ml; volume replacement consisted of 500 ml of packed red blood cells, 1000 ml of 5% albumin, and 2300 ml of crystalloid (Ringer's lactate and 5% dextrose in Ringer's lactate).

Arterial blood samples for measurement of plasma catecholamine levels by both radioenzymatic assay and high-pressure liquid chromatography were obtained before, during, and after anesthesia and surgery (Figure). Two independent catecholamine assays were used to verify individual values and trends in this uncommon condition. Hemodynamic data measured before, during, and after anesthesia and surgery are listed in the Table.

Discussion

Orthostatic hypotension of clinical significance occurs whenever the body is unable to maintain adequate cerebral perfusion because of a decrease in blood pressure on assuming the upright position (5). This may be caused by a decreased effective circulating blood volume, or it may be associated with neurogenic dysautonomia caused by drugs, malignancies, peripheral neuropathies, or Parkinson's disease (6). The patient whose case is reported above suffered autonomic dysfunction probably as a result of her associated metastatic breast carcinoma. Autonomic dysfunction with orthostatic hypotension associated with neoplasia is one of several different paraneoplastic syndromes (7, 8).

At times, the cause of the orthostatic hypotension associated with neurogenic dysautonomia is unknown and the condition is called idiopathic orthostatic hypotension (9, 10). If, in addition, there is central nervous system involvement, it is called the Shy-Drager syndrome (4).

The distinction between orthostatic hypotension caused by autonomic dysfunction related to a paraneoplastic syndrome and that caused by idiopathic orthostatic hypotension or the Shy-Drager syndrome is not always clear cut. It has been suggested that patients with idiopathic orthostatic hypotension without neurologic signs eventually develop the Shy-Drager syndrome (10), although other workers dispute this theory (9).

Orthostatic hypotension associated with carcinoma, idiopathic orthostatic hypotension, and the Shy-Drager syndrome are uncommon conditions. Autonomic neuropathy with orthostatic hypotension is a rare concomitant of neoplasia (8). The incidence of idiopathic orthostatic hypotension is unknown. Approximately 100 cases of the Shy-Drager syndrome were reported in the first decade following the initial description of the syndrome (1).

Anesthetic management of patients with autonomic dysfunction, whether central or peripheral, may be complicated by the loss of cardiovascular reflexes which commonly compensate for physiologic disturb-

FIGURE. Plasma catecholamine levels before, during, and after anesthesia and surgery: 1, awake, calm, immediately after arterial line insertion; 2, awake, calm, during insertion of pulmonary arterial catheter; 3, 1 minute after intubation; 4, 2 minutes after incision; 5, during surgery; 6, during surgery; 7, awake, calm, 10 minutes after surgery, in recovery room.

TABLE

Hemodynamic Values before, during, and after Anesthesia and Surgery

Time of day	Heart rate	Arterial pressure	Central venous pressure	Pulmonary arterial pressure	Pulmonary capillary wedge pressure	Cardiac output	Systemic vascular resistance	Pulmonary vascular resistance
	beats/min			torr		L/min	dynes·sec·cm^{-5}	
1500 (awake, before surgery)	100	120/70	7	25/10	9	5.9	1642	151
1530 (1 min after intubation)	102	130/80	7	28/21	14	5.6	2117	228
1608 (2 min after incision)	90	112/61	7	31/16	11	5.4	1770	283
1646 (during surgery)	87	107/65	2	22/11	10	3.4	2832	248
1824 (awake, 10 min after surgery)	83	128/78	5	25/14	8	4.7	2495	241

ance (3). Such patients may have relatively fixed heart rates, may be relatively unresponsive to atropine (parasympathetic involvement) (3), and may exhibit defective vasoconstriction (postural hypotension caused by norepinephrine depletion in adrenergic nerve terminals) (10) and, consequently, disordered baroreceptor reflexes (3). Sweating may be absent, pupillary reflexes sluggish, and control of respiration abnormal (3).

For the anesthesiologist, the importance of distinguishing between patients with the Shy-Drager syndrome and those with orthostatic hypotension caused by autonomic dysfunction without central nervous system involvement lies in their differing responses to pharmacologic intervention. Patients with the Shy-Drager syndrome, who seem to have normal peripheral sympathetic nervous systems with defective central control, respond normally to indirectly acting sympathomimetic agents (e.g., tyramine, ephedrine) and are not abnormally sensitive to directly acting adrenergic agents (e.g., norepinephrine, phenylephrine, isoproterenol) (9, 11). Patients with orthostatic hypotension due to peripheral autonomic dysfunction, however, are less responsive to indirectly acting amines and have exaggerated responses (denervation hypersensitivity) to directly acting agents (9).

The patient described above showed evidence of such denervation hypersensitivity before her operative procedure, and during surgery her blood pressure increased sharply following a 3-minute infusion of a small amount (33 μg) of the directly acting alpha-agonist phenylephrine, a response compatible with continued denervation hypersensitivity. If intraoperative hypotension had occurred, we would have treated it either with ephedrine or small amounts of phenylephrine. Caution in the use of adrenergic agents in patients with orthostatic hypotension due to autonomic dysfunction of any etiology is obligatory until the particular individual's responsiveness to such agents has been determined.

Before the operative procedure, only one relevant case report, (1) describing the anesthetic course of a patient with the Shy-Drager syndrome, could be located. This report described the use of an ultimately ineffective epidural anesthetic followed by general endotracheal anesthesia with methoxyflurane and N_2O in O_2, and an anesthetic course complicated by progressive arterial hypotension necessitating a continuous 4-hour infusion of phenylephrine during the anesthesia and operation.

We used fentanyl to avoid the risk of hypotension not infrequently seen with inhalation anesthetics even in physiologically normal patients. The apparent effectiveness of fentanyl in sedating our patient during the insertion of our monitoring devices prompted us to continue with fentanyl for maintenance of general anesthesia.

The use of regional anesthesia in a patient with progressive neurologic disease is controversial, and because hypotension is not uncommon even in physiologically normal patients following administration of spinal or epidural anesthesia, we felt the risks of severe hypotension in a patient with a defective autonomic nervous system outweighed possible benefits, and so avoided regional anesthesia.

The fact that this patient's neurologic status appeared to have been changing over the months immediately before surgery prompted us to avoid succinylcholine and to use a non-depolarizing relaxant instead, in view of reports of marked potassium efflux following succinylcholine use in patients with progressive neurologic disease (12) with possible cardiac arrhythmias resulting from sudden hyperkalemia following succinylcholine administration (13). However, succinylcholine has been used previously (1, 2) in patients with progressive autonomic dysfunction with no reports of associated cardiac disturbances.

The plasma catecholamine levels shown in the Figure indicate that a relatively small dose of fentanyl (5 μg/kg) along with 60% N_2O was effective in suppressing intraoperative catecholamine release. The fact that the patient's postoperative plasma catecholamine levels were markedly elevated above preoperative and intraoperative values indicates that she was indeed capable of releasing catecholamines but that such release was suppressed by her anesthetic. Catecholamine values and changes in the patient we report are similar in magnitude and direction to those reported previously for humans with coronary artery disease who were anesthetized with fentanyl, 75 μg/kg, and 100% O_2 (14). Those patients, in turn, had control (preoperative) catecholamine levels similar to both normal volunteers and to patients without heart disease (14, 15).

Exercise in physiologically normal man causes norepinephrine release (16). Both in patients with the Shy-Drager syndrome and those with orthostatic hypotension caused by autonomic dysfunction, standing or exercise fail to cause an increase in plasma levels of norepinephrine (9). Thus, suppression of catecholamine release during fentanyl anesthesia in such a patient may not reflect simply suppressed sympathetic function resulting from anesthesia. Nevertheless, in the patient we report, the decrease in plasma

catecholamine levels seen during relatively low-dose fentanyl anesthesia resembled that seen during high-dose fentanyl anesthesia in patients without autonomic dysfunction (14). More data on plasma catecholamine levels during anesthesia and operation in patients with autonomic dysfunction are needed to explain these changes.

Of the cardiovascular functions measured in the perioperative period in our patient, arterial blood pressure, central venous pressure, and cardiac output seemed roughly to parallel plasma catecholamine levels (Table and Figure). Systemic and pulmonary vascular resistances increased during anesthesia and operation, whereas plasma levels of catecholamines decreased. The reason for this paradox is not apparent.

A previous study (15) showed a positive correlation between changes in plasma catecholamine levels and mean arterial pressure during anesthesia and surgery, and concluded that changes in arterial pressure during surgical stress might be due to the pressor effects of released catecholamines. Adrenergic activation during surgical stress may be a response to afferent signals from the site of trauma (15). The apparent lack of adrenergic activation during surgery in our patient, who after surgery demonstrated the ability to mobilize catecholamines, together with her lack of pressor response to surgical stress and her condition on awakening from anesthesia, indicate that combined N_2O and low-dose fentanyl anesthesia were effective in suppressing afferent input from the site of surgical repair.

In summary, plasma catecholamine levels were assayed and hemodynamic function was monitored with a pulmonary arterial catheter before, during, and after anesthesia and operation in a patient with orthostatic hypotension due to autonomic dysfunction. Anesthesia with N_2O and a relatively low dose of fentanyl prevented both increases in plasma catecholamine levels and detrimental cardiovascular responses. Fentanyl and N_2O anesthesia thus provided cardiovascular stability and prevented adrenergic activation

during general anesthesia and surgery in a patient with orthostatic hypotension due to autonomic dysfunction.

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Treatment of Priapism with Ketamine and Physostigmine

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Priapism is persistent, painful, penile erection un-accompanied by sexual desire and unrelieved by sexual intercourse. It involves the corpora cavernosa but not corpus spongiosum or the glans penis. Priapism, if unrelieved in 24 to 36 hours, results in loss of sexual potency and the ability to attain orgasm in a significant percentage of affected patients (1). As the surgical treatment may be associated with loss of potency in 50% of patients (2), conservative measures to relieve priapism should be attempted in the early stages. Anesthesiologists are frequently requested to attempt to treat these patients with the administration of regional anesthesia or sedatives. Gale (3) reported on the successful use of intravenous ketamine (0.5 mg/kg) in the treatment of priapism in one patient. In our experience, utilizing ketamine alone, we noted partial success in two patients. In this report we present our experience in successfully treating two patients (one patient was treated twice) with ketamine and physo-stigmine. Addition of physostigmine apparently not only increased the effectiveness of ketamine but also decreased its unpleasant central nervous system side effects.

Case Reports

Case 1

A 25-year-old black man with a history of chronic renal failure was admitted to the hospital for renal hemodialysis. At the time of admission, drug therapy included propranolol, chlorothiazide, hydralazine, and allopurinol. Physical examination was unremarkable. The laboratory findings included blood urea nitrogen of 99 mg/dl, hemoglobin 10.5

g/dl, calcium 9.0 mg/dl, and potassium 4.8 meq/L. Four hours before the scheduled time of hemodialysis, he noted spontaneous painful penile erection. He claimed he had never experienced priapism earlier. An ice pack was placed around the penis and 75 mg of meperidine was given intramuscularly. He was given 5000 units of heparin IV before the hemodialysis. Following hemodialysis, the abnormal biochemical values returned to near normal levels. The prothrombin time was 12 seconds (control 12.2 seconds) and the partial thromboplastin time was 32 seconds. Hemoglobin electrophoresis did not reveal sickle cell disease or trait. Anesthesiology consultation was requested 8 hours following the onset of priapism. Physical examination revealed a well developed male in mild discomfort. The penis was erect and could not be moved to the side or downward. The corpora cavernosae were turgid. An intravenous cannula was inserted and 0.5 mg/kg of ketamine given. Soon the patient mumbled about seeing lights. About 10 minutes later partial penile flaccidity was noted. Within 5 minutes, physostigmine, in 0.5-mg increments totaling 1.5 mg, was given over a 10-minute period. Further gradual penile detumescence was noted over a period of 1 hour. Complete penile flaccidity was noted 90 minutes following the administration of ketamine. Since that time the patient has not had a recurrence of priapism.

Case 2

An 18-year-old black man was admitted to the hospital because of priapism. His past medical history was unremarkable. He was not taking any medications. He stated that painful penile erection was noted after the second sexual intercourse within an hour. He had had priapism for 4 hours before his admission. Examination revealed a young healthy man in moderate discomfort. The penis was erect and the corpora cavernosae were turgid. Laboratory findings were unremarkable except for a hemoglobin electrophoresis pattern positive for sickle cell trait. He was given meperidine, 75 mg IM, and an ice pack was placed around the penis. Three hours later, because of persistence of priapism, an anesthesiology consultation was requested. The patient was given, in 10-mg increments, ketamine to a total of 0.5 mg/kg IV. This caused moderate hallucinations and in 15 minutes, partial detumescence of the penis. Within 5 minutes, physostigmine, in 0.5-mg increments to a total of 1.5 mg, was given intravenously over a 10-minute period. The penis was completely flaccid 110 minutes following the start of ketamine administration.

The patient was subsequently readmitted to this hospital 2 months later because of another episode of priapism. The events that preceded the onset of the priapism were the same as had been reported during the earlier admission. The patient was given intravenous physostigmine in incremental doses of 0.5 mg, totaling 1.5 mg over a 10-minute period. Only partial flaccidity was noted in 30 minutes. Within 5 minutes, ketamine totaling 0.5 mg/kg was admin-

istered intravenously. Gradual detumescence resulted in total penile flaccidity 45 minutes following the administration of physostigmine.

Discussion

Patients with priapism, if not treated early, will develop impotency or loss of ability to attain orgasm. However, no treatment has reliably produced consistent penile flaccidity without causing adverse side effects. Failure to develop an effective therapy could be attributed to the fact that the pathophysiology of priapism is poorly understood. In most cases (60% to 80%) the etiology of priapism is unknown. In other cases, etiologic factors include sickle cell disease, sickle cell trait, perineal trauma, pelvic pathology, myeloproliferative disorders, psychotropic drugs, and certain cerebral conditions. As the pathophysiology of priapism is not clear, various investigators have observed varying degrees of success with their different treatments, which can be classified into conservative and surgical. Conservative treatment includes application of an ice pack, application of pneumatic cuff around the penis (2), sedation, general anesthesia, regional anesthesia, deliberate hypotension, and administration of estrogens, anticoagulants, and fibrinolytic agents (4). Surgical treatment includes needle puncture and irrigation of corpora cavernosae (5), unilateral and bilateral cavernosae-saphenous venous shunt (6, 7), cavernosum-spongiosum shunt (8), and cavernosum-dorsal vein shunt (9). Priapism, when it occurs in patients with sickle cell disease or myeloproliferative disorders, responds well to treatment of the underlying disease (10, 11). Surgical treatment of idiopathic priapism is more effective than conservative treatment. However, as the creation of venous shunt may result in loss of subsequent ability to achieve erection (2), conservative therapy should first be attempted in the early stages. Idiopathic priapism, if untreated, may last from 1 to 22 days (average 10 days) (3). Eriksson et al (1), in reviewing the case histories of 83 patients who had received conservative or surgical treatment, noted that patients who had treatment initiated within 24 hours of the onset of priapism had better results than did patients who were treated after 24 hours. On the basis of this review, the authors recommended that patients with this condition should be treated conservatively first and surgically later, but within 24 hours of onset of priapism.

Unfortunately, as the first episode of priapism is an embarrassing predicament to the patient, he often may not seek medical help for several hours. There-

fore, if conservative therapy is attempted, it must be effective. Gale (3) observed the development of penile turgescence in patients undergoing genitourinary surgery, whether they received regional or general anesthesia. In 25 patients who received 0.5 mg/kg of ketamine at the time of induction of anesthesia, none developed penile turgescence. In two patients who did not receive ketamine at the time of induction but who developed penile turgescence during the operation, partial detumescence was accomplished with the administration of 0.25 mg/kg of intravenous ketamine. In one patient with priapism (not simple turgescence), partial penile detumescence and complete flaccidity was accomplished with the intravenous administration of 0.25 and 0.5 mg/kg of ketamine. Based on this experience, Gale stated that administration of 0.5 mg/kg of intravenous ketamine might prevent, as well as treat, penile turgescence and priapism. In our experience, however, administration of 0.5 mg/kg of ketamine alone produced only partial penile detumescence in 2 hours in two patients with priapism that we observed (not reported here) in addition to the present two patients. Our present experience in three successful treatments of two patients indicates that a combination of ketamine with physostigmine is more likely to produce good results than reliance on ketamine alone.

How or why ketamine may be efficacious in management of priapism is not clear. Gale (3) stated that ketamine, by its dissociative property, might block the subconscious central response to peripheral penile stimulation. We speculate that priapism is the result of autonomic imbalance caused by intrinsic subconscious central stimulation. There are "polsters" in the arterial and venous ends of the corpora cavernosae (12). It is believed that priapism is caused by the failure of venous polsters to relax while arterial polsters contract and conceivably imbalance in the autonomic system could affect the proper functioning of these polsters. Ketamine may block the inciting central stimuli. In addition, ketamine causes both parasympathetic and sympathetic stimulation as clinically manifested by the fact that administration of ketamine is associated with increase in salivery secretions, heart rate, and blood pressure. Physostigmine stimulates the parasympathetic system, and this may aid in causing relaxation of vascular sphincters in corpora cavernosae (polsters). By altering the intrinsic tone of the autonomic nervous system, these two drugs seem to correct the pathophysiology of priapism.

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Anesthetic Considerations for the Patient with Homocystinuria

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Homocystinuria (alternatively, homocystinemia) is an inborn error of metabolism that is due to the failure of transsulfuration of the precursors of cysteine, an important constituent of the cross-linkages (1–4) in collagen. The affected person's weakened collagen explains most of the condition's clinical manifestations: dislocation of the lens; osteoporosis of long bones; lax ligaments; lengthened extremities; kyphoscoliosis; genu valgum; brittle, light-colored hair; flat feet; and malar flush (1–4). Lack of hyperextensibility of the joints differentiates the patient with homocystinuria from the patient with Marfan's syndrome (5). Another prominent but unexplained stigma of homocystinuria is mental retardation, which may be prevented by early diagnosis, dietary management, and pyridoxine administration. Although homocystinuria is an autosomal recessive disorder, the stigmata in an affected individual may range from few to many (1–4, 6). Its incidence is approximately 1:200,000 (1:40,000 in Ireland) (4).

The patient suffering from this inborn error excretes large amounts of homocystine and methionine. The diagnosis is usually confirmed by the presence of homocystine in the urine.

Affected persons may die at an early age due to thromboembolic phenomena (1–4). Breakage and fraying of the collagen in the media of vessels are thought to lead to the loss of endothelial cells from the vessel wall, which initiates intravascular clotting and platelet consumption (5, 7). Some investigators report that the affected person's platelets show vacuolization, are less adherent, and have abnormal aggregation (1, 4, 7); other investigators have not found these stigmata (8–10). It is also thought that the ho-

mocysteine in the blood activates the Hageman or contact factor (4).

With the recent advances made in diagnosis, prophylaxis, and management of homocystinuria, many patients who would have previously succumbed to the complications of the disease, now survive for much longer periods and may present themselves for anesthesia. Patients with homocystinuria may require general anesthesia on an emergency basis for unilateral or bilateral lens extraction for ectopia lentis, to which they are prone. Fatal episodes of thromboembolic phenomena may occur in these patients following general anesthesia. Consequently, we present a case report of a patient with homocystinuria, and we offer some suggestions that may be helpful in the management of similar cases.

Case Report

The patient was an 11-year-old girl with bilateral subluxed lenses and increasing intraocular pressure. Initially, she was treated conservatively with pilocarpine drops, mannitol (50 g) infusions, sedation, and bed rest. She did not respond to this regimen, and she was therefore scheduled for emergency surgery for bilateral lens manipulation and possibly lens extraction.

Before this current admission, the patient had been observed by the Orthopedic Department for her scoliosis and by the Neurology Department for mild mental retardation, poor development, and persistent headache. It was during the neurologic evaluation (8 months before her current admission) that the diagnosis of homocystinuria was made. The diagnosis was confirmed by the presence of large quantities of homocystine and methionine in her urine. Homocystine urinary level was 325 μg/24 hr (homocystine is not normally present in the urine) and methionine urinary level was 146 μg/24 hr (normal range 20 to 95 μg/24 hr). Plasma methionine levels were 39 μg/100 ml (normal range 1.3 to 3.9 μg/100 ml). There were no significant cardiopulmonary or renal problems. Her platelet count was 178,000/mm^3, prothrombin time 14/11 seconds, and partial thromboplastin time 22/24 seconds. Hematocrit was 33.9%. Electrocardiogram, serum electrolyte levels, and other laboratory data were within normal limits. Her weight was 38 kg. She was being given vitamin supplements of B$_6$, B$_{12}$, and folic acid for her homocystinuria.

The patient was premedicated with morphine sulfate, 4 mg IM; secobarbital, 40 mg IM; and glycopyrrolate, 0.2 mg IM. She was preoxygenated for approximately 3 minutes and a rapid sequence induction with intravenous atropine, 0.2 mg; pancuronium, 4 mg; and thiopental was carried out. Cricoid pressure was applied before tracheal intubation. Anesthesia was maintained with halothane and nitrous oxide and ventilation was controlled. Dextran 40 (500 ml)

was used for fluid administration along with 400 ml of dextrose/saline solution during the 2-hour and 20-minute procedure. Her anesthetic course was uneventful. Pancuronium was reversed with atropine, 1.0 mg, and physostigmine, 2.0 mg.

At the end of the procedure, she was transferred directly to the pediatric intensive care unit. She was given 40% oxygen by face mask and was heparinized with 3000 units subcutaneously every 12 hours. She was observed closely for signs of pulmonary emboli (tachypnea, dyspnea, chest pains, etc), but arterial blood gas tensions were always within normal limits. She was started on a low-methionine, high-cystine diet. She became ambulatory as soon as her surgery permitted it, and heparin was discontinued after 72 hours.

In the postoperative period, she was given pyridoxine, 500 mg, orally 4 times daily and dipyridamole (Persantin), 50 mg, orally 4 times daily. Forty-eight hours after surgery, she appeared to be doing well and was transferred to the pediatric floor. She continued to make good progress and was discharged home on the 5th postoperative day.

Discussion

It has been well demonstrated by McDonald et al (11) that patients with homocystinuria are prone to develop spontaneous thromboembolic phenomena. These phenomena are probably due to the activation of the Hageman factor by homocystine, resulting in increased adhesiveness of the platelets in the peripheral blood.

The specific defect in homocystinuria is believed to be due to a deficiency of the enzyme cystothionine synthetase in the liver with the deficiency of cysteine in the neonatal period, when the need for cysteine is great. Because of this enzymatic deficiency, plasma levels of methionine and homocystine are elevated and urinary excretion of homocystine is increased. When tested with nitroprusside (a test specific for homocystinuria), the patient's urine develops a characteristic magenta color. The urine may have a foul odor.

In animals, intravenously or intraperitoneally administered homocystine increases vascular endothelial cells in the circulating blood. Loss of such cells from the intima results in areas where the collagen is exposed and causes clotting to occur. Concommitantly, the number of circulating platelets decreases (7, 12). Harker et al (7) point out that in humans, effective treatment of these patients with dipyridamole mimics thromboembolism caused by prosthetic valves. They conclude that ". . . the underlying process of homocystinemic thrombosis probably involves

formation of platelet thrombus on altered nonepithelialized endarterial surfaces."

The case report of Vandresse et al (13) documents the seriousness of the vascular stigma of the patient with homocystinuria. An 8-year-old boy presented with mental retardation, dislocated lens, right hemiparesis since age 15 months, and the recent onset of left facial paralysis. A few days after a carotid angiogram, the child died of a posterior myocardial infarction confirmed at autopsy. In addition, the autopsy demonstrated old cystic lesions as well as new intravascular clotting of the carotid artery and new cerebral hemorrhages.

Management of homocystinuria consists of a diet low in methionine with supplements of cystine, choline, vitamin B_{12}, and folic acid. Large doses of pyridoxine have been shown to be of value in controlling and even reversing some of the symptoms. Homocystine has been found to increase platelet adhesiveness both in vivo and in vitro (11) and this is clearly related to the increased tendency to intravascular thrombosis. Pyridoxine, which acts as a co-enzyme in the metabolic pathway of methionine, has been shown to decrease platelet adhesiveness and thus lessen the risks of thromboembolic phenomena. If a patient is not receiving pyridoxine before surgery, it should be started after surgery as soon as possible.

In addition to the basic investigations routinely carried out in all cases, particular attention must be paid to the coagulation profile. The hematocrit, clotting time, prothrombin time, and partial thromboplastin time should be determined. In some institutions, postoperative follow-up studies of fibrin split products, platelet aggregation studies, and beta-thromboglobulin levels provide valuable information for effective therapy against intravascular thrombosis.

The goals of anesthetic management should be: (a) maintenance of high cardiac output and rapid circulation time, (b) reduction of blood viscosity and platelet stickiness, (c) reduction of vascular resistance and improvement of peripheral perfusion, (d) good venous return, (e) avoidance of dehydration and stress, and (f) rapid recovery from anesthesia with early postoperative ambulation. To achieve these goals, careful attention must be paid to the intraoperative administration of fluids (14). Preoperative hydration will minimize the risk of problems during induction of anesthesia. Crooke et al (15) have recommended the use of Macrodex (dextran with an average molecular weight of 70,000). We used dextran 40 because, like dextran 70, it diminishes platelet adhesiveness. An attempt to decrease the viscosity of the blood was

successful following the administration of generous amounts of dextran 40 and dextrose/saline solution. Dextrose solutions should be administered in addition to the dextran 40 because patients with homocystinuria are prone to develop hyperinsulinemia and hypoglycemia. As a further precaution against stasis of blood in the vulnerable venous system of calf muscles, the legs should be wrapped in elastic bandages or appropriate stockings. Intermittent changes in the position of the operating table when feasible during surgery should be carried out to facilitate peripheral venous return.

No particular drug is indicated or contraindicated in the anesthetic management of homocystinuria. Inhalation anesthetics are probably a better choice than narcotic analgesics as the latter could have residual respiratory depressant effects that could delay early postoperative ambulation. If nitrous oxide can be omitted from the anesthetic regimen, it may be theoretically advantageous as the possible hematopoietic depression and thrombocytopenia associated with long-term nitrous oxide administration might interfere with the body's clotting mechanisms in susceptible patients (16).

Although general anesthesia can induce postanesthetic thrombotic episodes, regional anesthesia is not without risk. Any nerve block that is performed in areas close to large- and intermediate-sized vessels, e.g., brachial plexus block, could initiate vascular damage culminating in thromboembolic phenomena. Spinal anesthesia, although not usually involving any significant blood vessels, could produce peripheral vascular stasis secondary to the sympathetic block produced. For the same reason, but to a lesser extent, epidural anesthesia is relatively contraindicated. Cerebral or carotic angiography with or without anesthesia is notorious for producing fatal thrombosis in these patients and should be avoided if possible. Following anesthesia, all patients should be observed for 36 to 48 hours in an intensive care facility. Further prophylaxis against coronary thrombotic episodes may be achieved by using dipyridamole (Persantine).

In summary, we have described a patient with homocystinuria who received general anesthesia for bilateral lens extraction. Homocystine, because of its

effect on platelet adhesiveness, may result in serious thromboembolic phenomena, especially following general anesthesia. To minimize these risks, special attention must be paid to fluid administration and the avoidance of dehydration and hypovolemia, the reduction in blood viscosity and platelet aggregation, and the maintenance of good venous return and the early ambulation of the patient. Recognition and control of this condition before surgery and judicious management after surgery could reduce the anesthetic morbidity and mortality of these already burdened patients.

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letters

TO THE EDITOR

Malignant Hyperthermia Associated with Isoflurane Anesthesia

To the Editor:

Malignant hyperthermia has been associated with most of the currently used inhalation anesthetic agents (1–3). The case described below is believed to be the first such occurrence with isoflurane anesthesia.

Case Report. A muscular 28-year-old Mexican-American, 91-kg man was scheduled for open reduction and internal fixation of a fracture of the right humerus following a gunshot wound sustained 1 year previously. No surgery was performed at that time. The patient was a heroin addict and had been on a methadone maintenance program until 1 week before admission. He also had a history of hepatitis with chronic elevation of plasma levels of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) (Table). The patient was not given an anesthetic. Preoperative physical examination was unremarkable. No one in the patient's family who had undergone any surgical procedures under general anesthetic had experienced any anesthesia-related problems.

The patient was premedicated with intramuscular meperidine, 50 mg, and hydroxyzine, 50 mg. On arrival in the operating room vital signs were as follows: blood pressure, 110/70 mm Hg; pulse, 70 beats per minute, respirations, 16 breaths per minute, and oral temperature, 36.8°C. Induction of anesthesia at 8:15 a.m. was with sodium thiopental, 675 mg, preceded by d-tubocurarine, 3 mg, and followed by succinylcholine, 100 mg. An 8-mm tracheal tube was inserted without difficulty under direct laryn-

goscopy. Anesthesia was maintained with a mixture of nitrous oxide and oxygen (3:2 L/min) and 2% isoflurane with manually assisted respirations at the rate of 12 to 16 breaths per minute. Vital signs remained stable for 2½ hours after induction when the patient suddenly developed a tachycardia of 130 beats per minute and tachypnea of 30 breaths per minute. Within a period of 5 minutes the esophageal temperature increased to 38°C and the soda lime absorber exhibited telltale signs of exhaustion and was changed. Over the next 20 to 25 minutes, the esophageal temperature rose to 40°C and the pulse rate increased to 180 beats per minute. The blood pressure was unchanged.

A tentative diagnosis of malignant hyperthermia was made and the following measures were initiated: ice packs were applied to all exposed areas, gastric lavage was commenced with iced saline, and lactated Ringer's solution was infused intravenously. Isoflurane and nitrous oxide were discontinued and the patient was hyperventilated with 100% oxygen. Arterial blood gas tensions were: P_{O_2}, 99 torr;

P_{CO_2}, 73 torr; pH 7.11; bicarbonate, 22 meq/L, and a base deficit of 5 meq/L. Dantrolene sodium, 200 mg, and sodium bicarbonate, 176 meq, were given intravenously. A Foley catheter was inserted and 1200 ml of urine was obtained which was normal in appearance and on subsequent examination did not contain myoglobin. The operation was completed in an expeditious manner at 11:30 a.m. and ½ hours later (12 noon) the temperature was 37°C and arterial P_{O_2} was 277 torr, P_{CO_2} 32 torr, pH 7.41, bicarbonate of 20 meq/L, and base deficit 3.7 meq/L. The temperature remained at 37°C. The patient was taken to the intensive care unit for further observation. Oral dantrolene, 90 mg, was administered 4 times a day for 3 days. The temperature remained between 37.2 and 37.7°C. The remainder of the postoperative course was unremarkable and the patient was discharged 5 days later.

This patient had, except for the absence of masseter rigidity during intubation, many of the abnormalities associated with malignant hyperthermia. The syndrome was suspected

TABLE

Plasma Enzyme and Electrolyte Levels before, during, and after Anesthesia

| | Normal values for LAC-USC Medical Center | Preoperative (9/28/81) | Values in patient | | | | |
| | | | Intraoperative | | Postoperative | | |
			10:45 a.m. (2 hr)	Noon (4 hr)	24 hr	48 hr	5 days
CPK (U/L)	25–200	143	378	4790	4290	2065	187
LDH (U/L)	200–500	508	613	618	731	632	516
SGOT (U/L0	5–40	144	97	139	110	179	59
SGPT (U/L)	5–40	293	181	210	170	54	96
Aldolase (U/L)	7				36		
Serum							
Potassium (meq/L)	3.7–5.1	4.4	6.8	4.0	3.8	3.9	3.7
Calcium (mg/dl)	8.6–10.3	10.5	7.6	8.5	8.5	8.4	8.7
Creatinine (mg/dl)	0.4–1.3	1.0	1.6	1.2	1.0	0.9	0.9
BUN (mg/dl)	6–25	14	16	11	11	10	10

before the temperature began to increase when tachycardia, tachypnea, and increased carbon dioxide production, as evidenced by exhaustion of the soda lime, occurred. The condition was confirmed by the increase in temperature and the occurrence of combined metabolic and respiratory acidosis.

The chronic elevation of plasma levels of liver enzymes in our patient was probably due to the fact that he was a drug addict with chronic active hepatitis rather than a manifestation of his susceptibility to malignant hyperthermia. Unfortunately, a muscle biopsy was not obtained, but despite its absence we feel that the findings are compatible with a diagnosis of malignant hyperthermia.

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Isoflurane and Malignant Hyperthermia

To the Editor:

In vitro (1, 2) and in vivo (Murphy FL Jr, Nelson TE, Strobel GE, Jones EW. A comparison of halothane, isoflurane, enflurane, and fluroxene in triggering malignant hyperthermia in susceptible swine. Abstracts of Scientific Papers. Annual Meeting of the American Society of Anesthesiologists, 1973, pp 181–2.) data suggest that isoflurane may act to trigger ma-

lignant hyperthermia. The following case report describes such an instance.

Case Report. The patient was a muscular, 17-year-old black man who was 183 cm tall and weighed 94 kg. Except for the present injury, a bucket-handle tear of the lateral meniscus of the right knee incurred while playing football, he was in good health. He had never had surgery, and there was no family history of anesthesia-related complications. Results of routine preoperative blood tests and urinalysis were normal. The patient was schedule for a right arthroscopy-arthrotomy and lateral meniscectomy.

At 10:35 a.m. the patient received meperidine, 35 mg, promethazine, 25 mg, and atropine, 0.4 mg. He was brought to the operating room (room temperature that day averaged 18.9°C) at 11 a.m. Immediately before induction, blood pressure was 160/95 torr, pulse rate 112 beats per minute, oral temperature 36.7°C, and axillary temperature 37°C. At 11:10 a.m., 300 mg of thiopental was given followed by 0.5% to 2.5% isoflurane in 67% nitrous oxide (total flow of 6 L/min). Five minutes later, cephalothin, 2 g, was given intravenously. Pressure and pulse decreased to 100/60 torr and 78 beats per minute, respectively, and were stable until 11:30. At that time, axillary temperature had decreased slightly to 36.7°C. Between 11:30 and 11:35, succinylcholine 0.2% was infused and arthroscopy begun. By 11:35, blood pressure had increased to 135/95 torr and pulse rate to 118 beats per minute. Succinylcholine infusion ceased at 11:35 and blood pressure and pulse rate decreased to 120/75 torr and 104 beats per minute, respectively, and were stable until 11:55. At that time, a decision was made to proceed with an arthrotomy. At 11:55 succinylcholine again was infused to facilitate orotracheal intubation which was accomplished without difficulty, but with an associated increase in pulse rate to 125 beats per minute. By 12:00 to 12:05 p.m., temperature had increased slightly to 36.9°C and the blood pressure and pulse rate decreased to 105/65 torr and 120 beats per minute, respectively. The isoflurane concentration was reduced to 2% at 12:10 with a

slight subsequent increase in blood pressure.

Temperature now began to rise reaching 37.5°C by 12:15 and 38.2°C by 12:30. Movement or shivering had been noted, and malignant hyperthermia diagnosed. All anesthetics were discontinued at 12:30, and the tourniquet was released at 12:40. Surgery was completed by 12:45, at which time temperature had risen to 39°C. The carbon dioxide absorber was noted to be hot to touch and the absorbant was turning purple. A nonrebreathing system was substituted for the circle absorption system with a 7-L/min delivery of oxygen.

During the next 15 minutes, the bladder and stomach were irrigated with iced saline, and dantrolene and sodium bicarbonate were infused. The patient was further cooled with ice applied to the surface of the body. The temperature stabilized at 40.6°C and then decreased. Other subsequent therapy included dexamethasone, methylprednisolone, 50% glucose, and crystalloid infusion. Further doses of dantrolene (total dose 120 mg) and sodium bicarbonate (total dose 700 meq) were administered. The latter was given to relieve a severe metabolic acidosis diagnosed from an arterial blood sample obtained at approximately 1:00 p.m. (pH 6.78; P_{CO_2} 120 torr; BE −21 meq/L; P_{O_2} 256 torr). Serum potassium level was 6.9 meq/L.

By 1:10 the patient was responding to commands but was agitated, in part because of the continued presence of the endotracheal tube. Transient pulmonary edema was associated with the administration of large amounts of fluid and sodium bicarbonate, but otherwise recovery occurred without further incident.

Dantrolene, 25 mg, was given orally 3 times a day for the first 3 postoperative days. Serum creatine phosphokinase (CPK) values exceeded 6000 mU/ml for the first two postoperative days, decreasing to 4325 mU/ml on day 3, and to 1900 mU/ml on day 4. Lactic dehydrogenase (LDH) and serum glutamic oxaloacetic transaminase (SGOT) levels were modestly increased to 420 to 430 and 160 to 230 mU/ml, respectively, on the first two postoperative days and thereafter decreased. The patient

was discharged on the fifth postoperative day.

Several factors may have contributed to the rapid rise in temperature seen in this patient. Prime among these is the administration of isoflurane. Another factor is succinylcholine (total dose 100 mg), which was associated with a marked increase in pulse rate (20 to 40 beats/min) with each administration. One might also consider that other drugs given in the preoperative period (e.g., promethazine or atropine) acted as triggering agents, but this would seem unlikely in view of the delay between their administration and the appearance of hyperthermia. Also, generation of heat might have been increased by the large muscle mass possessed by this youth and by the shivering associated with the steepest portion of the rise in temperature. Heat loss may have been limited by the patient's smaller than normal surface-to-volume ratio, by atropine premedication, and by surgical drapes which covered nearly all surfaces that might have been used to eliminate heat.

We conclude that isoflurane, perhaps in concert with other factors, possibly triggered malignant hyperthermia. An awareness that this rare malady may occur during isoflurane anesthesia is essential to the recognition and prompt treatment of this potentially disastrous event.

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* Reprint requests to Dr. Eger.

Pseudohypotension

To the Editor:

Controlled hypotension facilitates clipping of intracranial aneurysms by decompressing the aneurysm at the time the clip is applied. With aneurysms of the carotid circulation, the risk of systemic hypotension may be avoided by ipsilateral carotid compression. To do this, the anesthetist reaches up under the drapes, through the tangle of ventilator and monitoring equipment, and palpates the carotid artery in the neck. The artery is then intermittently compressed against the cervical vertebrae coincident with the surgeon's manipulation of the aneurysm. We recently cared for two patients in whom this maneuver was associated with profound hypotension. In one, who was 26 weeks pregnant, mean arterial pressure decreased to 22 torr. In neither case was there a change in pulse rate or in the shape of the arterial wave form. Although we initially speculated about various possible reflex mechanisms, the absence of change in heart rate mitigated against such a conclusion. We normally place the arterial line in the dorsalis pedis artery but in both

of these cases the cannula was placed in the ipsilateral radial artery. A review of the anatomy of the neck showed that in compressing the carotid artery low in the neck it is also possible to compress the ipsilateral subclavian artery. In a subsequent patient, this was confirmed (Figure).

In addition to making our colleagues cognizant of this form of pseudohypotension, we suggest that the arterial line be placed in the dorsalis pedis artery or, failing this, in the contralateral radial artery.

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The Silent Ventilator

To the Editor:

The Narco Airshields "Ventimeter Controller" is a widely used and relatively trouble-free ventilator for operating room use. It is quiet while in normal operation and is equipped with a loud, insistent disconnect alarm.
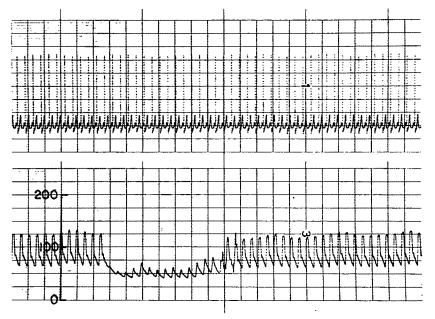
FIGURE. Top, Electrocardiogram shows no change in heart rate. Bottom, Dramatic drop in blood pressure with carotid compression is shown. Note that this is not rounded wave form usually seen with damping.

Recently, the timer valve failed in a 1-year-old Ventimeter Controller in our operating room. This occurred within one cycle and the ventilator ceased cycling with the bellows in the fully extended position. As there was no loss of pressure, the disconnect alarm did not sound, and as the Ventimeter is so quiet in operation, the noise level in the anesthesia area did not abruptly drop (a useful indicator of ventilator failure of older, noisier machines).

We are writing to remind those who use the Ventimeter Controller of the limitations of the alarm systems (loss of pressure only) and to remind anesthetists who may come into contact with this instrument for the first time that cessation of cycling noise may not be as useful a secondary alarm as it is with other ventilators. Listening to the gas flow within the patient's trachea with a pretracheal or esophageal stethoscope remains the simple mainstay of careful ventilatory monitoring.

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Isobaric Spinal Anesthesia

To the Editor:

We were interested to read the paper by Levin and colleagues (1). As the paper questions work from this department, suggesting that isobaric solutions are preferred for lower limb and perineal surgery, we would like to comment.

Our studies (2, 3) have shown that isobaric tetracaine solutions produce sensory level blocks with a mean maximum height limited to the low thoracic level irrespective of drug dosage. Levin and colleagues found that isobaric solutions spread considerably higher. It is important to consider why there is this difference in results.

We almost always used 25-gauge

needles and injected in solutions at 1 ml/5 sec; these were prepared by diluting 1% tetracaine to 0.5% with saline. Levin and co-workers used 22-gauge needles, diluted with cerebrospinal fluid (CSF) and did not quote a speed of injection although the faster rate likely with a larger needle might increase spread. The difference in patient position between their work and ours is irrelevant because the spread of isobaric solutions has been shown to be unaffected by position (3).

Dilution with "warm" CSF rather than "cold" saline might be important, but we would expect a cooler solution to have a higher initial baricity and thus spread further in the supine patient. However, the difference between results shows the reverse of that which might be expected from a "thermal" explanation, so it would seem that that may be discounted.

What of the "bulk" effect of using CSF as a diluent? A paper presented at the 1982 annual meeting of The American Society of Regional Anesthesia by Foelschow, Batra, and Mulroy from The Mason Clinic in Seattle pointed out that prior removal of CSF increases cephalad spread of hypobaric tetracaine. Perhaps withdrawal of CSF for dilution has a similar effect with other solutions.

The difference between the results from the two centers is almost certainly due to differences in methodology. We would certainly agree with their conclusion that other factors besides baricity affect the intrathecal spread of local anesthetic solutions.

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Epidural Analgesia in the Presence of Herpes Simplex Virus (Type 2) Infection

To the Editor:

Herpes simplex virus (HSV) type 2 infection afflicts 0.5% to 1% of pregnant women (1). The stress of labor and delivery can provoke an exacerbation of the infection. Infants delivered through the vaginal canal of mothers afflicted with HSV type 2 infection are exposed to the risk of contracting systemic viral infection (2). Therefore, it has been recommended that delivery in these parturients be accomplished by cesarean section (2). Some of these patients might wish to remain awake and therefore would like regional anesthesia. Anesthesiologists, however, are faced with the question of whether or not regional anesthesia is a safe procedure in these patients. In response to a leading question concerning the safety of regional anesthesia in these patients, Phillips (3) expressed his opinion that although regional anesthesia by itself may not cause dissemination of infection, primary HSV type 2 might sometimes cause meningitis (2). In our review of the literature, however, we noted only one documented case of generalized HSV type 2 infection, including the meninges, in a patient with severe immune deficiency syndrome. HSV type 2 infection has predilection for the perineal area and the cervix, whereas epidural anesthesia is generally performed in the midlumbar area. Regional anesthesia is frequently performed in the presence of acute infections such as perineal abscess or chorioamnionitis without increased incidence of dissemination of infection. Even in the presence of acute viral infections such as herpe zoster, some clinicians recommend the performance of epidural sympathetic block of the involved dermatone to prevent the development of postherpetic neuralgia (4). In their series, Perkins et al (4) did not observe an increased incidence of disseminated infection. Based on these considerations, we have performed continuous epidural anesthesia in more

than 30 pregnant patients with HSV type 2 infection with good results and no complications.

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Chloroprocaine: Neurotoxicity and Formulations in Perspective

To the Editor:

The recent publication in this journal by Moore et al (1) contains incorrect and misleading information as well as innuendos that necessitate clarification of facts concerning commercially available 2-chloroprocaine (Nesacaine and Nesacaine-CE) solutions. The number of "additional" adverse experiences and the nature of the products' formulation have been misrepresented.

The paper purports to present "four additional cases" of prolonged neural blockade following use of 2-chloroprocaine for epidural anesthesia. In reality, five cases are presented in the paper, three of which have been extensively discussed at several scientific meetings and in print (2). The reference cited (2) is included in the paper by Moore et al, but recognition of previous reporting of these cases is ignored by these authors. Specifically, Moore's cases 2, 3, and 5 were presented previously in a "Nesacaine Update" (2), as cases 3, 13, and 11, respectively, and do not represent new information or, indeed, additional cases. The first case reported

by Moore et al (1) came to our attention after the last "Nesacaine Update" was distributed in 1981, and, therefore, could not have been presented previously even though the incident occurred in 1977. Pennwalt has been refused access to the details of Moore's case 4, which apparently occurred in The Netherlands, even though the details of the case were known to the authors of the paper in question. This case presents a particularly interesting problem as Nesacaine and Nesacaine-CE are not marketed in The Netherlands, and the formulation and source of the 2-chloroprocaine solution used are not disclosed in the paper. The formulations of 2-chloroprocaine distributed in the United States are Nesacaine and Nesacaine-CE, which have a long established history of use with Food and Drug Administration (FDA) approval.

The long history of 2-chloroprocaine in this country under the close regulation of the FDA is presented by Moore et al (1) in a fragmentary manner which can only confuse the reader, rather than present information useful to the discerning anesthesiologist. The *Physician's Desk Reference* (PDR) is referred to by Moore et al as though it were an all-inclusive source of information on drugs, their formulations, formulation changes, and composition. Those familiar with the PDR over more than a decade of use will know that the PDR was originally a vehicle for disseminating information and marketing of drugs, although, in more recent times, it has become a compilation of package inserts to be used as a ready reference for physicians. However, even currently, not all drugs are included in the PDR, and of those included, not all dosage forms or formulations may be included. To use the PDR from 1957 to the present as an all-inclusive source of information on formulations of drugs, including 2-chloroprocaine, can only result in superficial knowledge and lead to erroneous conclusions or speculations. Two authoritative sources of information regarding formulations of ethical drugs, such as Nesacaine, are the FDA and the company marketing the drug. To seek information from sources other than authoritative ones can only result in imperfect information. In the case of Nesacaine and Nesacaine-CE, the quantitative aspects of formula-

tions have always appeared in the products' labeling and served as a ready source of information for those who choose to use them.

The reality of formulation changes in 2-chloroprocaine preparations marketed in the United States can be easily summarized. In 1955, the product was sold as a sterile powder under the brand name of Halestyn, to be reconstituted with sterile diluent before use. In 1956, three solutions of 2-chloroprocaine were marketed under the brand name of Nesacaine. The composition of the three solutions is shown in the Table. The 2-chloroprocaine is, of course, the active drug, the sodium bisulfite is an antioxidant, the methylparaben is a preservative, and the NaCl is added in sufficient quantity to establish isotonicity with physiologic systems. Note that only the 3% solution was originally available for caudal or epidural use, as it did not contain preservative. In 1959, a 2% solution was made available without the methylparaben for use in caudal anesthesia. The only significant changes that occurred during the period from 1959 to the present were the addition of solutions containing epinephrine, which were later discontinued due to insufficient demand by physicians to warrant continued marketing of the product. Several minor changes in packaging, i.e., size of single-dose containers (100-ml vials to 30- or 50-ml vials) and changes from vials to ampules, etc, occurred over the years to accommodate use in the clinic. In 1964, the 2% and 3% solutions, not containing methylparaben, were labeled as "Nesacaine-CE" (CE refers to caudal-epidural) to aid in distinguishing them from Nesacaine containing the preservative, not intended for epidural use. The concentration of the sodium bisulfite (0.2%) has remained constant from 1956 to the present, and, although the pH of the final solutions is not printed on

TABLE

Composition of Three Solutions of 2-Chloroprocaine Marketed in 1956 as Nesacaine

2-Chloro-procaine HCl	Sodium bisulfite	Methylparaben	NaCl
1%	0.2%	0.1%	0.6%
2%	0.2%	0.1%	0.4%
3%	0.2%	—	0.2%

the label, it should be evident that the pH would be in a constant range (2.7 to 4.0) since 1956, and has been, as the final concentration of sodium bisulfite is the major determinant of pH of the solution. Similarly, the level of methylparaben (0.1%) has remained constant since 1956 in those solutions containing the preservative.

Moore et al (1) questioned the instruction "not to be used for caudal or epidural block," contained in the PDR, for the 1% and 2% Nesacaine solutions from 1963 through 1970 and stated "The reasons for such limitations have yet to be revealed." The answer should be obvious; they contained preservative. Only the 2% and 3% solutions without preservative are, and were, recommended for such use.

The two papers cited by Moore et al (3, 4), reporting a high incidence of thrombophlebitis in 1956, were the result of use of methylparaben-containing solutions by the intravenous route. Since that time, extensive use (T.A.R. Palas, H. R. Gerber, M. Schnapp, et al, unpublished observations, 1980) of 2-chloroprocaine solutions without preservative by this route has been reported without adverse effects. Most individuals would agree that the presence of the preservative may have contributed to the early cases of thrombophlebitis, rather than concluding: "The etiology of these was never determined."

Often the time between publications by a single author allows for reasonable changes in opinions due to assimilation of additional scientific information. The paper by Moore et al (1) contains no span of time, within itself, but yet presents the contradictory views that: "Animal investigation supports that the likelihood of neuropathy resulting from the subarachnoid injection of epinephrine is infinitesimal" in one paragraph, and, in another paragraph, "Therefore, until the etiology of neuropathy associated with its [2-chloroprocaine] use in humans is specifically identified (animal data, because of species differences, cannot be extrapolated to humans), and. . . ." Indeed, the principal author of the paper (D.M.) has elsewhere cited evidence (5) from animal studies to support his views of neurotoxicity of 2-chloroprocaine in humans. This obvious lack of consistency in consideration of experimental animal studies, rather than presenting all scien-

tific information objectively to the anesthesiology community, can only lead to misunderstanding and nonobjective consideration of available information.

The authors of any scientific publication of adverse reactions to drugs have an obligation to the profession they are addressing to at least attempt to place the observations reported in their appropriate context of clinical practice. The paper by Moore et al (1) attempts to leave the reader with the impression that serious adverse reactions have occurred only with 2-chloroprocaine, while references are clearly available in the literature, including those cited by Moore et al, reporting qualitatively similar adverse clinical experiences with all agents in this pharmacologic class. This biased presentation by Moore et al is clearly in contrast to the candid and widespread disclosure of all pertinent information on adverse reactions and research findings available to Pennwalt, in print, and at scientific meetings, including conferences and a symposium (6) sponsored by Pennwalt, to place before the anesthesiologist the relevant information necessary for the individual physician to reach his or her own knowledgeable conclusion. Pennwalt will continue to objectively inform the anesthesiology community of such information.

In summary, the paper by Moore et al (1) does not present substantive new information useful to the responsible anesthesiologist in making decisions as to the best treatment for his or her patient. The use of all drugs is associated with both benefit and risk to the patient. Publications that contribute to a further understanding of the merits and risks of drugs in their proper context are to be encouraged, whereas publication of fragmentary information and old data described as new, can only lead to misinterpretation and confusion.

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To the Editor:

The letter of Stephen Riggi, is appreciated and enlightening as was a previous letter and an article from the Pennwalt Corporation (1, 2).

Also, an apology is extended for not recognizing that our cases 2, 3, and 5 had been presented previously in the "Nesacaine Update" as cases 3, 11, and 13 (3). In that publication, these cases were listed under "duration" of the neuropathy as "?," 6 to 10 weeks, and 1 month, respectively. Therefore, we interpreted this to mean the complications were transient. Inasmuch as the neuropathy in our patients has existed 6, 3, and 1½ years, respectively, and is evidently permanent, we did not consider the cases to be the same as any in the "Pennwalt Update."

Furthermore, as the statements in the *Physician's Desk Reference*, as well as in the package inserts that accompany drugs, are presumably written by the pharmaceutical companies, it is surprising to read Riggi's statement that they present "superficial knowledge and lead to erroneous conclusions or speculations." Does this imply that the statement, "Solutions of Nesacaine and Nesacaine-CE do not injure nervous tissue and are not irritating to other tissues in the concentration recommended," which has appeared in that publication from 1971 through 1982, is erroneous (4, 5)?

Also, it was surprising to find that he considers our cases to be presented in a "fragmentary manner" (4). It was thought that they included the significant facts, in comparison to those presented by Pennwalt regarding not only chloroprocaine but other local anesthetic drugs (1, 3). In the "Nesacaine Update," question marks appeared where our cases revealed the facts (3, 4). Furthermore, all the cases presented by us and other anes-

thesiologists have occurred since 1976 (4, 6, 7). It is doubtful that the regional block trays and the drugs prepared by reputable pharmaceutical companies used in the cases reported after 1976 (4, 6, 7) could have contained tissue irritants (detergents, methylparaben, and so forth), as could those used in cases of neuropathy that resulted before that date (1). However, although Riggi is correct in stating that methylparaben in high concentrations has been shown to be a neurolytic drug in animals (8, 9) and therefore has been removed from 2% and 3% chloroprocaine solutions for caudal and epidural block (Nesacaine-CE), he evidently considers the 2 mg/ml of sodium bisulfite that these solutions contain to be innocuous. This drug was shown to be a tissue irritant in 1937 (10), and in 1982 the subarachnoid injection in rabbits of 0.4 to 0.6 ml of 0.2% sodium bisulfite (the same concentration as in the chloroprocaine solution) produced motor and sensory impairment (11). Also, solutions of chloroprocaine that contained sodium bisulfite (3% Nesacaine-CE) produced hindlimb paralysis in dogs when injected subarachnoidally (12). Conversely, in sheep it did not (13). If, in the dogs, the bisulfite was not responsible for the paralysis, then it either had to be the chloroprocaine or a combination of it and the bisulfite.

Finally, Riggi questions the formulation of chloroprocaine used in the case from The Netherlands. It was Pennwalt's 3% Nesacaine-CE.

In conclusion, we again wish to thank Riggi, for his letter. He and other employees (1-3) of the Pennwalt Corporation have indeed shed light on the chloroprocaine neuropathy controversy. It should be noted that the necessity for timeliness in this response precluded obtaining the reactions of the other authors of our article (4) to Riggi's letter.

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Errant Guide Wire: The Problem

To the Editor:

The recent report by Parker and DeVore (1) of difficulty with guide wire insertion during internal jugular (IJ) cannulation, proposes potentially dangerous conclusions. They report an apparently uncomplicated IJ venipuncture, in which they were unable to advance a flexible guide wire via this relatively straight venous path. Cope (2) offered the most logical explanation for this problem: a venipuncture that appears correct but in fact is not. Our first response to the report of Parker and DeVore is to rephrase their initial point:

A smoothly placed IJ vein guide wire should easily advance down the superior vena cava. When it does not, it should be assumed that the needle for venipuncture or the guide wire has taken an errant

course. Persistence with the cannulation attempt under those circumstances is unadvisable.

Of even more concern is the authors' relative disregard for the fragility of guide wires (3). Excessive manipulation of guide wires has resulted in wire fragmentation and elaborate retrieval procedures that deal with wire embolization have been described (4). The safety guide wire (5) has gained widespread use as a result of the wire fragmentation problem and the inherent difficulties in the manufacture of wires (6). We would also rephrase the authors' second point:

Guide wires are delicate devices and will not accept abuse under any circumstances.

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To the Editor:

The concern expressed by Schwartz, Ellison, and Jobes for safe central cannulation techniques is appreciated. In their reply to our report they state we "were unable to advance a flexible guide wire via this relatively straight venous path." A review of our letter, however, reveals no such statement (1). The problem we encountered was the inability to pass an introducer over a guide wire definitely placed in the internal jugular vein (IJV). We feel confident the

guide wire was correctly placed because (a) immediately preceding guide wire insertion, aspiration of the fully advanced unstyleted catheter was remarkable for free flow of venous blood and (b) insertion of the wire through this catheter was accompanied by the minimal amount of resistance usually associated with this procedure.

The problem these authors fail to address, which was the major point of our report, is that even smooth advancement of a guide wire in a caudad direction in a properly cannulated IJV does not guarantee a central intravenous course. If resistance is encountered advancing the introducer after successful guide wire placement, consideration should be given to the wire following an aberrant intravascular (e.g., cephalad) or even extravascular pathway (1). We would, therefore, add to the authors' first response that even after smooth guide wire placement, resistance to catheter advancement may also make further cannulation attempts inadvisable. Furthermore, if the decision is made to attempt to develop a fascial plane inhibiting advancement of an introducer over a correctly placed guide wire, it should be done gently and with caution.

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Inappropriateness of Statistical Methods Used in Evaluating Postanesthetic Hepatic Injury

To the Editor:

The recent article by Harper et al

(1) contains statistical inadequacies and statements that should be noted. First, postanesthetic hepatic injury was graded from 0 to 5 and thus is an ordinal scale variable. One-way analysis of variance and regression analysis were reported as the methods used to analyze these data. These statistical methods assume interval or ratio scale data. Hence, the conclusions drawn by the authors in this study should be viewed with caution. It is also inappropriate to report means and standard errors when summarizing ordinal scaled data. More appropriate statistical methods for analyzing and summarizing ordinal scale data should have been used (2).

A better experimental protocol would have required equal allocation of animals to all groups. This would have resulted in equal precision and would have allowed more powerful statistical comparisons between experimental groups.

In addition, two typographical errors were noted. In table 2, "n = 1" should read "n = 11," and, on page 80, the lower abdominal surgery group (group VI) is mislabeled as group VII.

Finally, contradictory statements were made in the article. In one place, the text states that "Injury after lower abdominal surgery (group VI) was not significantly different from that after ligation of the hepatic artery (group II) or upper abdominal operation (group V)," whereas in another place it is stated that "Ligation of the hepatic artery (group II) resulted in significant hepatic injury when the anesthetic agent was halothane (table 1)."

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REFERENCES

1. Harper MH, Collins P, Johnson BH, Eger IE II, Biava CG. Postanesthetic hepatic injury in rats: influence of alterations in hepatic blood flow, surgery, and anesthesia time. Anesth Analg 1982;61:79–82.
2. Hays WL. Statistics for the social sciences. 2nd ed. New York: Holt, Rinehart and Winston Inc, 1973:81–90, 760–803.

To the Editor:

Although the criticism of the statistical methods used is valid, a second analysis of the data using the Kolmogorov-Smirnov test (1) did not alter the appearance of significant differences among groups ($p < 0.001$). That is, our conclusions remain those stated in the original paper.

Also, we do not believe the statements concerning hepatic artery ligation or abdominal surgery are contradictory. Lower abdominal surgery, upper abdominal surgery, and hepatic artery ligation produced hepatic injury when halothane was the anesthetic used. No difference in the extent of injury induced by the different operations could be demonstrated. However, ligation of the hepatic artery did not produce significant hepatic injury when the anesthetic agent was enflurane, isoflurane, or thiamylal. We still would conclude that "Ligation of the hepatic artery (group II) resulted in significant hepatic injury when the anesthetic agent was halothane."

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REFERENCE

1. Siegel S. Nonparametric statistics for the behavioral sciences. New York: McGraw-Hill, 1956:127–36.

book REVIEWS

Recovery Room Care, edited by J. S. Israel and T. J. DeKornfeld, Springfield, IL, Charles C Thomas, Publisher, 1982, 334 pp, $37.50.

Drs. Israel and DeKornfeld have put together an excellent book that should be read by health professionals in anesthesiology, intensive care, surgery, and nursing.

Its 334 pages comprise 13 chapters written by 20 expert contributors, through which the reader is easily guided from the design of the recovery room (recommended for architects), equipment and safety, and management and staffing to the clinical aspects such as criteria for patient care, emergency diagnosis, ventilatory and circulatory disorders, and fluid replacement.

Chapters 10 to 12 deal with the postoperative management of the cardiac patient, special pediatric problems, and neurosurgical aspects of recovery room care, respectively. These three chapters bring to light the unique problems of patients within these categories; some institutions have recognized the special care required by these patients and have established separate units for their postoperative care. This book will hopefully encourage the creation of more of these units.

Although it is difficult to single out any portion of this book, "Postoperative Management of the Cardiac Patient," by Peter B. Kane, deserves special mention. With the continuous increase in open heart surgery, the postoperative care recommended in this chapter will help eliminate unnecessary morbidity and mortality.

Maybe a short chapter 14 could have been added to discuss the presently available computerized patient care systems, including those that offer a "close loop" for infusion of fluids and blood. Probably, such a chapter does not belong in a book dealing strictly with recovery room care, but this book exceeds the limits imposed by its title.

Finally, a good review of "Legal Considerations" will help prevent unnecessary anxiety and aggravation if some of the simple rules outlined in this chapter are followed.

In summary, this is a book that is well written, well edited, easy to read, and one that belongs in many libraries.

Herbert Ferrari, MD
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Pathophysiology of Shock, Anoxia, and Ischemia, edited by R. A. Cowley and B. E. Trump, Baltimore, The Williams & Wilkins Co., 1982, 710 pp, $75.00.

This large multiauthored tome is a collaborative editorial effort between a cardiac surgeon and a cellular pathologist. It succeeds in presenting a comprehensive picture of the pathophysiology and treatment of shock, ischemia, and anoxia. The book is divided into four sections and eight parts. The sections cover basic pathophysiology, shock, central nervous system injury, and vascular insufficiency. Each of the eight parts has a summary that explains the relevance of the material and places it into clinical perspective.

The authors begin with the hypothesis that shock and related conditions are primarily states of energy depletion and invoke secondary ion shifts to explain the concept of general cellular injury. They characterize both reversible and irreversible cellular injury at the ultrastructural level and conclude that the mitochondrion is the site of alterations that render the cell irreversible. There is an excellent review of some of the newly discovered vascular mediators including the prostacycline-thromboxane system and the lysosomal hydrolases and their ultimate effects on cellular function. These effects are related to the pathology and pathophysiology of the major organ systems including the liver, lung, kidney, and gastrointestinal tract. This altered physiology is related to the clinical setting by an excellent section on the current therapy of shock. Included are chapters on cardiac arrest, trauma, the use of corticosteroids, infection, and transfusion.

The stated aim of this text is to overcome the distance, both practical and philosophical, between the basic scientist and the clinician. To meld these two disparate worlds, this book freely crosses the borders between laboratory investigation and bedside care. It takes what is new and original from a research standpoint and applies it to the familiar clinical picture of shock in a way that lends a new appreciation of clinical pathophysiology. For too long there has existed a gap, both in language and practice, between researchers and clinicians interested in shock. This long-awaited text presents a comprehensive picture of the major problems in shock, ischemia, and anoxia from which to

build a rational background for work in this area.

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Cardiac Anesthesia, edited by T. J. Conahan III, Reading, MA, Addison-Wesley Publishing Co., Inc., 1982, 340 pp, $29.95.

This book consists of 15 chapters, almost all of which were written by members of the faculty at the University of Arizona.

The quality of the chapters varies widely, as is often the case with multiauthored texts. I found the chapters, "Natural History and Clinical Diagnosis of Acquired Valvular Heart Disease" and "Cardiac Catheterization," particularly well done and readable. Unfortunately, the chapters dealing with anesthetic considerations for both valvular and coronary artery disease were, at best, disappointing. The chapter, "Special Considerations for Coronary Artery Disase" is 12 pages, one of which is devoted to pointing out the importance of the hemoglobin molecule in oxygen transport.

According to the preface, this book was intended as a basic text for the resident and practitioner. I am afraid the title is misleading and the book misses the mark. It would be an excellent basic text for a medical student interested in cardiac surgery, but is both too simple and incomplete for a resident interested in the complex field of cardiac anesthesia.

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A Guide for Authors

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Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

Illustrations must be good quality, unmounted glossy prints, usually 12.7 by 17.3 cm (5 by 7 in), but no larger than 20.3 by 25.4 cm (8 by 10 in).

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   Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687-90.

2. Corporate Author

   The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119-25.

   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224-5.

Books and Other Monographs

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

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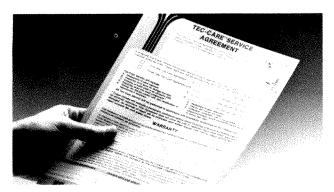
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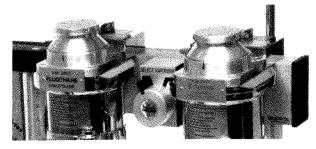
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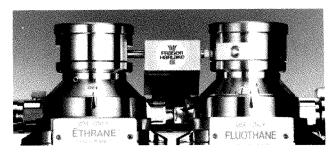
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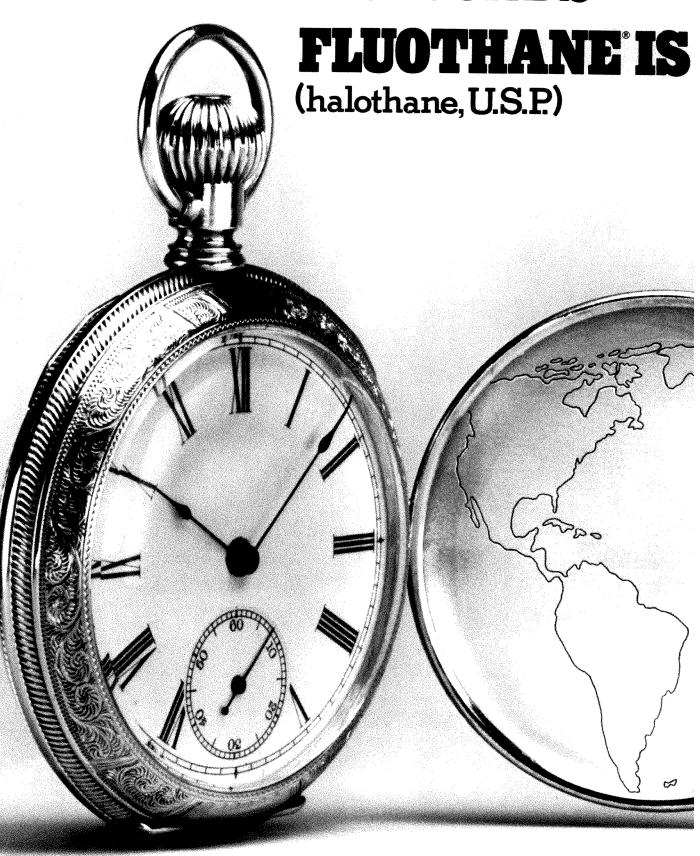
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□ FLUOTHANE has been more widely investigated than any other inhalation anesthetic.

□ The FLUOTHANE experience shows association with hepatotoxicity to be extremely rare.[1] According to conclusions drawn from the United States National Halothane Study and other studies,* unexplained jaundice following anesthesia with halothane "...was a rare occurrence (approximately 1:30,000 administrations) and...the overall safety record of the anesthetic was excellent."[2]

□ FLUOTHANE "...is nearest to the ideal [inhalation anesthetic] presently available for children of all ages."[3]

□ FLUOTHANE has been recommended as the "anesthetic of choice"[4] for asthmatics.

□ And, of particular benefit in geriatrics and cardiovascular surgery: Excessive respiratory depression is rarely a problem with FLUOTHANE. Nor does it produce an increase in salivary or bronchial secretions.

*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., et al.: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

References:
1. Bunker, J.P., et al.: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology 43:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists. April 20-22, 1979, Richmond, VA.

Ayerst. Ayerst Laboratories New York, N.Y. 10017

(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:

$$ F-\overset{\overset{\textstyle F}{|}}{\underset{\underset{\textstyle F}{|}}{C}}-\overset{\overset{\textstyle Br}{|}}{\underset{\underset{\textstyle H}{|}}{C}}-Cl $$

The specific gravity is 1.872-1.877 at 20°C, and the boiling point (range) is 49°C – 51°C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20°C. The blood/gas coefficient is 2.5 at 37°C, and the olive oil/water coefficient is 220 at 37°C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), up to 0.00025% ammonia (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation.

FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

It has been reported that in genetically susceptible individuals, the use of general anesthetics and the muscle relaxant, succinylcholine, may trigger a syndrome known as malignant hyperthermic crisis. Monitoring temperature during surgery will aid in early recognition of this syndrome. Dantrolene sodium and supportive measures are generally indicated in the management of malignant hyperthermia.

Adverse Reactions. The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P., stabilized with 0.01% thymol (w/w), and up to 0.00025% ammonia (w/w).　　**7197/R82**

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Anesthesia and Analgesia

EDITORIAL

SCIENTIFIC ARTICLES

Contents

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INJECTION IM or IV

ATIVAN® (LORAZEPAM) IV
INJECTION IM or IV

DESCRIPTION: Ativan* (lorazepam) Injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal *failure*. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately postinjection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure.* Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure.* EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (See WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan* (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX* Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.
For IM or IV injection.

Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

Wyeth Laboratories
Philadelphia, PA 19101

C13117-1   7/31/80

When it comes to infection control, this Ohio® mask has a clear advantage.

You probably already use a disposable circuit. Perhaps disposable filters and tracheal tubes, too. So why not complete your infection control program with the Ohio Disposable Anesthesia Breathing Mask.

Especially when the Ohio Disposable Mask helps you combat nosocomial infection. And contributes to your insight into your patient's status.

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The Ohio Disposable Mask is transparent. It maximizes visual access to your patient.

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Use the Ohio Disposable Mask once... and simply throw it away. Then, you don't have to worry about insufficient cleaning and sterilization. Or that the mask might pick up pathogens prior to use.

Gently conforms to your patient's face.
The Ohio Disposable Mask is available in three sizes to fit a wide variety of facial features.

The soft, malleable cushion holds its shape to help provide a tight seal and minimize facial marking. And the shape of the cone makes holding the mask easier, less tiresome for you.

Call your Ohio representative today. And find out how this new disposable mask makes a clear-cut contribution to your infection control program.

Ohio Medical Products
A Division of Airco, Inc.
3030 Airco Drive, P.O. Box 7550, Madison, Wisconsin 53707

Xylocaine®
(lidocaine hydrochloride)
4% Sterile Solution

Before prescribing or administering, please consult complete product information, a summary of which follows:

CONTRAINDICATIONS: Lidocaine hydrochloride sterile solution is contraindicated in patients with a known history of hypersensitivity either to local anesthetics of the amide type or to other components of the sterile solution.

PRECAUTIONS: The safety and effectiveness of lidocaine hydrochloride depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for various anesthetic procedures.

The lowest dosage that results in effective anesthesia should be used. Injection of repeated doses of lidocaine hydrochloride may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug or its metabolites. Tolerance varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status. Lidocaine hydrochloride should also be used with caution in patients with severe shock or heart block.

As with all injections of local anesthetics, retrobulbar injection should always be made slowly and with frequent aspirations.

Solutions to which a vasoconstrictor has been added should be used with caution in the presence of diseases which may adversely affect the patient's cardiovascular system. Serious cardiac arrhythmias may occur if preparations containing a vasoconstrictor are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other related agents.

Lidocaine hydrochloride should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine HCl.

Local anesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precaution should be taken to avoid this type of interaction.

The safety of amide local anesthetics in patients with malignant hyperthermia has not been assessed, and therefore, those agents should be used with caution in such patients.

Drowsiness following lidocaine hydrochloride injection is usually an early indication of a high blood level of the drug and may occur following inadvertent intravascular administration or rapid absorption of lidocaine.

ADVERSE REACTIONS: Adverse reactions may result from high plasma levels due to excessive dosage, rapid absorption or inadvertent intravascular injection. Such reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system. A small number of reactions may result from hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

CNS reactions are excitatory and/or depressant, and may be characterized by nervousness, dizziness, blurred vision and tremors, followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest. The excitatory reactions may be very brief or may not occur at all, in which case the first manifestations of toxicity may be drowsiness, merging into unconsciousness and respiratory arrest.

Toxic cardiovascular reactions to local anesthetics are usually depressant in nature and are characterized by hypotension, myocardial depression, bradycardia and possibly cardiac arrest.

Treatment of a patient with toxic manifestations consists of assuring and maintaining a patent airway, supporting ventilation with oxygen, and assisted or controlled ventilation (respiration) as required. This usually will be sufficient in the management of most reactions. Should a convulsion persist despite ventilation therapy, small increments of anticonvulsive agents may be given intravenously. Examples of such agents include benzodiazepine (e.g., diazepam), ultrashort acting barbiturates (e.g., thiopental or thiamylal) or a short acting barbiturate (e.g., pentobarbital or secobarbital). Cardiovascular depression may require circulatory assistance with intravenous fluids and/or vasopressors (e.g., ephedrine) as dictated by the clinical situation.

Allergic reactions may occur as a result of sensitivity either to local anesthetics or to other components of the sterile solution. Anaphylactoid type symptomatology and reactions, characterized by cutaneous lesions, urticaria, edema, should be managed by conventional means. The detection of potential sensitivity by skin testing is of limited value.

HOW SUPPLIED: Xylocaine (lidocaine hydrochloride) 4% Sterile Solution: 5 ml ampule, package of 10; 5 ml prefilled sterile disposable syringe.

ASTRA®
Astra Pharmaceutical Products, Inc.
Worcester, Massachusetts 01606

THE ANXIETY OF INDUCTION

CALM THE APPREHENSION WITHIN MINUTES WITH INJECTABLE VALIUM (diazepam/Roche) I.V.

You've seen the signs of anxiety hundreds of times. Palpitations. Tremulousness. Diaphoresis. Hyperventilation. Ordinary patients about to undergo an extraordinary ordeal: the physical and emotional traumas of neuromuscular blockade, anesthesia and surgery.

When you administer an antianxiety agent to these patients just before the procedure, you want a prompt, predictable anxiolytic response. And that is exactly what you achieve with Injectable Valium (diazepam/Roche) I.V.

Usually within three minutes, patients grow noticeably calmer after an intravenous injection of Valium.[1,2]

In most instances the patient falls into a light sleep, yet can still be easily aroused to respond to your instructions. This allows you to proceed directly with intubation, neuromuscular blockade and/or anesthesia. Other anxiolytics lack the rapid action of Injectable Valium I.V., and may take up to 20 minutes or more to produce adequate sedation—a long time to wait before beginning the procedure. The rapid sedative action of Injectable Valium I.V. gives you the control you need in the critical minutes before intubation. Dosages of concomitantly administered narcotic analgesics should be reduced by at least one-third and administered in small increments. In some cases, the use of a narcotic may not be necessary.

Ready to use—needs no reconstitution or refrigeration In further contrast to other injectable anxiolytics, which may require dilution before being used, Injectable Valium I.V. needs no reconstitution. Do not mix or dilute Valium with other drugs or solutions in syringe or infusion flask; administer slowly directly into a large vein, or inject slowly through the infusion tubing as close as possible to the vein insertion site. Take at least one minute for each 5 mg (1 ml).

During storage, there is no need to refrigerate Injectable Valium—another advantage over other injectable agents.

DIMINISH RECALL OF THE PROCEDURE WITH INJECTABLE VALIUM (diazepam/Roche) I.V.

Recall of endotracheal intubation or other psychologically disturbing events associated with anesthetic induction and surgery can be largely prevented with Injectable Valium I.V.

A survey of the literature shows that 2586 of 2707 patients (95%) had partial or total lack of recall when Injectable Valium (diazepam/Roche) I.V. was given as premedication for procedures in cardiac and plastic surgery, fracture reductions, gynecologic surgery, oral surgery and ophthalmic surgery.[3] The anterograde amnesia produced after an intravenous injection of Valium usually begins to take effect within three minutes, peaks within 10 minutes and persists for 20 to 60 minutes.[2,4-7]

Minimal effect on cardiac and respiratory function
A review of published reports involving more than 12,000 patients administered Injectable Valium—including patients with coronary artery disease—shows that clinically significant blood pressure changes, alterations in basal circulatory parameters or increased incidence of hypotension, tachycardia or bradycardia are rare when recommended procedures for dosage and administration are followed. Clinically significant respiratory depression is also rare with Injectable Valium I.V. in subjects without respiratory disease (0.3% incidence in more than 12,000 patients).[3]

Facilities for respiratory assistance, however, should be readily available. When administering Injectable Valium I.V. to the elderly, to very ill patients or to patients with limited pulmonary reserve, lower doses (usually 2 mg to 5 mg) and slow increase in dosage should be used because of the possibility that apnea and/or cardiac arrest may occur. Concomitant use of barbiturates or other CNS depressants increases depression with increased risk of apnea. As with most CNS-acting drugs, patients should be cautioned against drinking alcohol or operating hazardous machinery.
So when anxiety mounts in the face of induction, choose the I.V. agent with a rapid, predictable anxiolyic effect...

RAPIDLY AND PREDICTABLY CALMED WITH

INJECTABLE VALIUM® I.V.
(diazepam/Roche) Ⓘ

Ready-to-use, 2-ml Tel-E-Ject® disposable syringes
2-ml ampuls, 10-ml vials ⎱ 5 mg/ml

See next page for references and summary of product information.

References: 1. Diazepam and lorazepam in anaesthesia. *Drug Ther Bull* 17:19-20, Mar 2, 1979. **2.** Conner JT *et al: J Clin Pharmacol* 18:285-292, May-Jun 1978. **3.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **4.** George KA,

Dundee JW: *Br J Clin Pharmacol* 4:45-50, Feb 1977. **5.** Dundee JW, Pandit SK: *Br J Pharmacol* 44:140-144, Jan 1972. **6.** Gregg JM, Ryan DE, Levin KH: *J Oral Surg* 32:651-664, Sep 1974. **7.** Clarke PRF *et al: Br J Anaesth* 42:690-697, Aug 1970.

INJECTABLE VALIUM®(diazepam/Roche)Ⓘⓥ

Please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less), prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence, can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; re-administer if necessary; not recommended for long-term maintenance therapy. If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), i.e., phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcohol withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, administer I.V. slowly; for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

For one of medicine's most demanding skills... one of medicine's most dependable agents

Ethrane® (enflurane)

precise control...stability of heart rhythm...
reduced relaxant requirement...prompt, smooth recovery
...organ toxicity rare or nonexistent

Ethrane (enflurane) **10** years of experience confidence safety

Ohio Medical Anesthetics

For complete use information, please see following page.

Ethrane® (enflurane)

DESCRIPTION

ETHRANE (enflurane) (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether) (CHF$_2$OCF$_2$CHFCl) is a nonflammable inhalation anesthetic agent. The boiling point is 56.5°C at 760 mm Hg. and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10} P = A + B/T \qquad A = 7.967$$
$$B = -1678.4$$
$$T = °C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20°C is 1.3025-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C.

Enflurane is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary even in the presence of ultraviolet light. Enflurane is stable to strong base and does not decompose in contact with soda lime and does not react with aluminum, tin, brass, iron or copper. The partition coefficients of enflurane at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ETHRANE (enflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70 percent nitrous oxide—30 percent oxygen, and 1.17 in 30 percent nitrous oxide—70 percent oxygen.

Induction and recovery from anesthesia with enflurane are rapid. Enflurane has a mild, sweet odor. Enflurane may provide a mild stimulus to salivation or tracheobronchial secretions. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia can be changed rapidly by changing the inspired enflurane concentration. Enflurane reduces ventilation as depth of anesthesia increases. High PaCO$_2$ levels can be obtained at deeper levels of anesthesia if ventilation is not supported. Enflurane provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during enflurane anesthesia. Enflurane anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with enflurane and injected with epinephrine containing solutions to achieve hemostasis in a highly vascular area (transsphenoidal surgery), it is recommended that 2 micrograms per kilogram (2 µg/kg) of epinephrine may be injected subcutaneously over a 10 minute period. This may be repeated up to 3 times per hour.

Example: Up to 10 ml of 1:100,000 epinephrine containing solution (10 µg/ml) may be injected subcutaneously over a 10 minute period in a 50 kilogram patient judged to have ordinary tolerance to epinephrine administration. No more than 30 ml of 1:100,000 epinephrine containing solution (10 µg/ml) should be administered to such a patient per hour. The concomitant administration of lidocaine enhances the safety of the use of epinephrine during enflurane anesthesia. This effect of lidocaine is dose related. All customary precautions in the use of vasoconstrictor substances should be observed.

Example Two: Alternatively, up to 20 ml of 1:200,000 epinephrine containing solution (5 µg/ml) may be substituted for 10 ml of 1:100,000 solution in the above example.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with enflurane. The NON-DEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 5 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of enflurane.

Biotransformation of enflurane in men results in low peak levels of serum fluoride averaging 15 µM/L. These levels are well below the 50 µM/L threshold level which can produce minimal renal damage in normal subjects. However, patients chronically ingesting isoniazid or other hydrazine containing compounds may metabolize greater amounts of enflurane. Although no significant renal dysfunction has been found thus far in such patients, peak serum fluoride levels can exceed 50 µM/L, particularly when anesthesia goes beyond 2 MAC hours. Depression of lymphocyte transformation does not follow prolonged enflurane anesthesia in men in the absence of surgery. Thus enflurane does not depress this aspect of the immune response.

Enflurane 0.25 to 1.0 percent (average 0.5 percent) provides analgesia equal to that produced by 30 to 60 percent (average 40 percent) nitrous oxide for vaginal delivery. With either agent, patients remain awake, cooperative, and oriented. Maternal blood losses are comparable. These clinical approaches produce normal Apgar scores. Serial neurobehavioral testing of the newborn during the first 24 hours of life reveals that neither enflurane nor nitrous oxide analgesia is associated with obvious neurobehavioral alterations. Neither enflurane nor nitrous oxide when used for obstetrical analgesia alters serum BUN, creatinine, uric acid or osmolality. The only difference in the use of these two agents for obstetrical analgesia appears to be higher inspired oxygen concentration that may be used with enflurane.

Analgesic doses of enflurane, up to approximately 1 percent, do not significantly decrease the rate or force of uterine contraction during labor and delivery. A slowing of the rate of uterine contraction and a diminution of the force of uterine contraction is noted between the administration of 1 and 2 percent delivered enflurane, concentrations somewhere between 2 and 3 percent delivered enflurane may abolish uterine contractions. Enflurane displaces the myometrial response curve to oxytocin so that at lower concentrations of enflurane oxytocin will restore uterine contractions, however, as the dose of enflurane progresses (somewhere between 1.5 and 3 percent delivered enflurane) the response to oxytocin is diminished and then abolished. Uterine bleeding may be increased when enflurane is used in higher concentrations for vaginal delivery or to facilitate delivery by Cesarean section; however, this has not been demonstrated within the recommended dosage range (see DOSAGE AND ADMINISTRATION section). Mean estimated blood loss in patients anesthetized for therapeutic abortion with 1 percent enflurane in 70 percent nitrous oxide with oxygen is approximately twice that noted following therapeutic abortion performed with the use of a local anesthetic technique (40 ml versus 20 ml).

INDICATIONS AND USAGE

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Enflurane may be used to provide analgesia for vaginal delivery. Low concentrations of enflurane (see DOSAGE AND ADMINISTRATION) may also be used to supplement other general anesthetic agents during delivery by Cesarean section. Higher concentrations of enflurane may produce uterine relaxation and an increase in uterine bleeding.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS)
Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics
Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentrations usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged enflurane anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to depth of anesthesia. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

PRECAUTIONS

The action of nondepolarizing relaxants is augmented by ETHRANE (enflurane). Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from neuromuscular blockade will be longer in the presence of enflurane than when halothane or nitrous oxide with a balanced technique are used.

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. Enflurane should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug.

In susceptible individuals, enflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure (it should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc. The syndrome of malignant hyperthermia secondary to enflurane appears to be rare; by March 1980, 35 cases had been reported in North America for an approximate incidence of 1/726,000 enflurane anesthetics.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO$_2$ absorption system (hot canister). PaCO$_2$ and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., enflurane), administration of intravenous dantrolene, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. Renal failure may appear later, and urine flow should be sustained if possible.

Swiss ICR mice were given enflurane to determine whether such exposure might induce neoplasia. Enflurane was given at ⅛, ¼, and ½ MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice who were given the same background gases, but not the anesthetic.

Exposure of mice to 20 hours of 1.2 percent enflurane causes a small (about ½ of 1%) but statistically significant increase in sperm abnormalities. In contrast to these results, in vitro approaches to this study of mutagenesis (Ames test, sister chromatid exchange test, and the 8-azaguanidine system) have not shown a mutagenic effect of enflurane.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to enflurane. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

ADVERSE REACTIONS

1. Malignant hyperthermia
2. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
3. Hypotension and respiratory depression have been reported.
4. Arrhythmias, shivering, nausea, and vomiting have been reported.
5. Elevation of the white blood count has been observed.

OVERDOSAGE

In the event of overdosage, the following action should be taken:
Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using
a) vaporizers calibrated specifically for enflurane;
b) vaporizers from which delivered flows can easily and readily be calculated.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by enflurane and that enflurane does not alter heart rate. The use of anticholinergic drugs is a matter of choice.

Surgical Anesthesia: Induction may be achieved using enflurane alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the enflurane mixture. In general, inspired concentrations of 2.0-4.5 percent enflurane produce surgical anesthesia in 7-10 minutes.

Surgical levels of anesthesia may be maintained with 0.5-3 percent enflurane. Maintenance concentrations should not exceed 3 percent. If added relaxation is required, supplemental doses of muscle relaxants are to be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of enflurane concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Analgesia: Enflurane 0.25 to 1.0 percent provides analgesia for vaginal delivery equal to that produced by 30 to 60 percent nitrous oxide. These concentrations normally do not produce amnesia. See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section.

Cesarean Section: Enflurane should ordinarily be administered in the concentration range of 0.5 to 1.0 percent to supplement other general anesthetics. See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section.

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INDICATIONS: INAPSINE (droperidol) is indicated:
to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures;
for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia;
in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE* (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.
If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.
The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.
If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.
Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.
Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.
When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.
Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.*

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.
Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.
Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).
When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated respiratory arrest could occur. Elevated blood pressure, with or without preexisting hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved. Vital signs should be monitored routinely.
Usual Adult Dosage
I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.
II. Adjunct to General Anesthesia
  Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
  Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
  If INNOVAR* injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.
III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
  Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.
IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

HOW SUPPLIED: 2 ml. and 5 ml. ampoules-packages of 10; 10 ml. multiple-dose vials—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10
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EDITORIAL

Is Atracurium an Ideal Neuromuscular Blocking Drug?

THE INTRODUCTION of pancuronium in the United States in 1972 represented the last muscle relaxant to be approved for clinical use by the U.S. Food and Drug Administration. The search for the "ideal muscle relaxant" has persisted for more than 20 years by several investigators. Before designing a new drug, the ideal muscle relaxant had to be defined.

Savarese and Kitz (1) felt two new types of muscle relaxants were needed. One type is a non-depolarizing muscle relaxant with an onset time and duration of action similar to that of succinylcholine, but without all its well known problems. BW 785U seemed to meet these qualifications (2). However, because of significant histamine release (3), clinical trials with BW 785U were terminated. The search for a neuromuscular blocking drug that has all the advantages, but none of the disadvantages of succinylcholine, thus persists.

Savarese and Kitz (1) also suggested that a drug with an intermediate duration of action (i.e., between succinylcholine and pancuronium) would add flexibility to our muscle relaxant administration practices. Desirable characteristics should include lack of cumulative and cardiovascular effects. Also, a drug that is metabolized and/or is not dependent on the kidney for its elimination would be helpful, as all currently available non-depolarizing muscle relaxants primarily depend on the kidney for their elimination.

Recently, two such muscle relaxants have undergone clinical trials in the United States. Although described in several publications in Europe, vecuronium (ORG NC 45) was first described in the American literature by Fahey et al (4) with an accompanying editorial by Savarese (5). Vecuronium fits most of the characteristics Savarese and Kitz (1) identified as desirable for an intermediate-acting neuromuscular blocking drug. Vecuronium is a non-depolarizing muscle relaxant with a duration of action ½ to ⅓ that of pancuronium. It has little or no cumulative effect and no apparent cardiovascular action. Also, vecuronium is not markedly dependent on the kidney for its elimination and probably is excreted primarily unchanged in the bile (6).

In this issue, Katz et al (7) and Basta et al (8) describe the first American clinical trials with another non-depolarizing muscle relaxant with an intermediate duration of action, atracurium. Using similar anesthetic techniques, but different methods of stimulation and quantifying neuromuscular transmission (i.e., electromyogram versus force displacement), both groups found the duration of action of atracurium was indeed shorter than that of pancuronium. Also, no cumulative effect was observed; that is, the same dose could be given repetitively at the same point in recovery with no increasing duration of action. However, there are differences between the two studies. For example, Basta et al (8) found an onset time (time from injection to peak effect) of atracurium, 0.60 mg/kg, to be 1.3 minutes, whereas Katz et al (7) found the onset time from the same dose to range from 2.5 to 4 minutes. Payne and Hughes (9) found an onset time of 1.2 minutes from the same dose of atracurium. Although different methods were used to quantitate neuromuscular transmission, the reason for the relatively longer onset time in the Katz et al (7) study is not apparent. However, the onset time of atracurium certainly appears to be shorter than that of pancuronium. The ultimate test will be the time required from administration of atracurium until adequate conditions exist for endotracheal intubation, which can only be determined by many clinicians under a variety of clinical settings.

Another slight difference between the two studies is evident with the cardiovascular data. Katz et al (7) found no cardiovascular effects from atracurium using the Riva Rocci technique and the electrocardiogram. Basta et al (8), using a radial artery line and tachograph, found a small, but significant increase in heart rate and decrease in blood pressure with doses of atracurium larger than 0.50 mg/kg. Despite these differences, such small cardiovascular changes are probably clinically insignificant. The prediction that atracurium is not dependent on the kidney or liver for its elimination remains to be tested in patients.

The Katz et al (7) study illustrates that the incremental or cumulative method for producing a dose-

response curve may differ significantly from data obtained when a single intravenous bolus of atracurium is given. The incremental method of establishing a dose-response curve has obvious advantages because fewer subjects are required than with the traditional single-bolus injection method. Donlon et al (10) found that the incremental-dose method and the conventional single-bolus injection produced nearly identical dose response curves with both pancuronium and d-tubocurarine. The reason the incremental-dose method produces a blockade of lesser magnitude with atracurium is probably because of its rapid metabolism and, possibly, its redistribution. Significant recovery from neuromuscular blockade from the initial dose has occurred when subsequent doses are given. Thus, in establishing dose-response curves, the methodology is far more critical with shorter-acting drugs like atracurium and vecuronium (11) than with longer-acting drugs such as pancuronium or d-tubocurarine.

A comparison of atracurium and vecuronium is inevitable. Superficially, atracurium appears to have neuromuscular blocking characteristics similar to those of vecuronium (4, 7–9). Because experimental techniques differ from group to group, a precise comparison of the two drugs can only occur when the same investigators use identical experimental conditions to study the drugs. Such studies have yet to be published. Still, both muscle relaxants generally meet the original characteristics described by Savarese and Kitz (1) as desirable for non-depolarizing muscle relaxants of intermediate duration of action. Thus, in this author's opinion, atracurium and vecuronium both represent a significant increase in our flexibility as far as muscle relaxant administration is concerned, and fulfill the requirements necessary for a neuro-

muscular blocking drug of an intermediate duration of action. At this point, it appears that research should now be directed toward finding a non-depolarizing muscle relaxant with an onset time and duration of action similar to that of succinylcholine.

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Clinical Pharmacology of Atracurium Besylate (BW 33A): A New Non-depolarizing Muscle Relaxant

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Atracurium, a new non-depolarizing neuromuscular blocking agent, was studied in 70 patients anesthetized with fentanyl, thiopental, and nitrous oxide-oxygen. The dose found to produce 95% twitch inhibition (ED_{95}) was 0.2 mg/kg. The onset time from injection to maximum depression of twitch was 4.0 minutes at this dose; the duration to 95% recovery was 44.1 minutes. Twice the ED_{95} dose (0.4 mg/kg) had an onset time of 1.7 minutes and a duration of 63.5 minutes. No cardiovascular effects were observed in this dosage range. At higher doses (0.5 and 0.6 mg/kg) arterial pressure decreased 13% and 20% and heart rate increased 5% and 8%, respectively. Sixteen patients received at least four successive doses of atracurium. No clinically significant cumulative effect could be shown when recovery from 25% to 75% of control twitch height was compared for initial and final doses in the series. Atracurium spontaneously decomposes at physiologic pH via the Hofmann elimination reaction and may also undergo ester hydrolysis independent of plasma cholinesterase. These proposed pathways of inactivation may explain the lack of cumulative effect and the drug's intermediate duration of action. Based on the results of this study, atracurium offers several clinical advantages and should undergo more extensive clinical trials.

Key Words: NEUROMUSCULAR RELAXANTS: atracurium.

THE CLINICAL need for new neuromuscular blocking drugs of various durations of action (short, intermediate, and long) continues today. One would ideally like these new agents to be non-depolarizing and have high potency, rapid onset, and no cardiovascular side effects. In addition, such new drugs should not release histamine, should lack cumulative properties, should undergo metabolism to pharmacologically inactive and nontoxic metabolites, and should be usable equally well in normal subjects and in patients with renal or hepatic insufficiency. Atracurium besylate (BW 33A), a new non-depolarizing relaxant synthesized and developed by Stenlake (1), appears to possess many of these desirable characteristics. In Britain it has been shown, first in animals by Hughes and Chapple (2) and subsequently in anesthetized patients by Payne and Hughes (3), to be a potent non-depolarizing relaxant devoid of cardiovascular side effects. In addition, atracurium's metabolic pathways may be unique insofar as initial studies suggest that the molecule may decompose at physiologic pH to inactive metabolites by two mechanisms: (a) spontaneously by Hofmann elimination, and (b) by an enzymatic ester hydrolysis not dependent on plasma cholinesterase (2) (see Fig 1). Atracurium is currently available for clinical trials in this country. The present study was designed to confirm the results of previous investigations and to quantitate in greater detail, time of onset of action, degree of cumulation, if any, and extent of any cardiovascular effects in healthy anesthetized patients during nitrous oxide-narcotic-barbiturate anesthesia.

FIG 1. Proposed pathways for inactivation of atracurium by Hofmann elimination reaction and ester hydrolysis.

Methods

The study included 70 patients, 42 men and 28 women, A.S.A. class I, 18 to 58 years of age, who were having elective surgery; all patients gave institutionally approved written informed consent. Before anesthesia, blood samples for determination of dibucaine number and plasma cholinesterase activity were drawn from each subject. This was done to ascertain whether a correlation might exist between the duration of neuromuscular block produced by atracurium and plasma cholinesterase activity. As atracurium is an ester and because in vitro measurements suggest that the drug is not metabolized by plasma cholinesterase (2), this was considered an important aspect of the study.

Fasting subjects were premedicated 1 to 1.5 hours before surgery with oral diazepam, 0.15 mg/kg, and intramuscular morphine, 0.1 mg/kg. Anesthesia was

induced with intravenous fentanyl, 4 to 8 μg/kg and thiopental, 5 to 10 mg/kg. Tracheal intubation was accomplished using topical lidocaine. Controlled ventilation was used to maintain normal arterial blood gas tensions. Anesthesia was maintained using nitrous oxide and oxygen (4 L/2 L) and additional thiopental and/or fentanyl as needed. In a few patients it was necessary to use enflurane (0.5% inspired) after recovery from the initial dose of atracurium to maintain adequate levels of anesthesia without administration of high doses of fentanyl or thiopental. These patients were included in analysis of all twitch data.

Heart rate (by tachygraph), radial arterial pressure, esophageal temperature, and electrocardiogram were continuously monitored. Neuromuscular function was monitored by recording responses of the ulnar nerve-adductor pollicis system using 200 to 250 g of resting tension of the thumb. Responses were evoked by repetitive train-of-four stimulation (2 Hz for 2

seconds repeated every 10 seconds) applied to the ulnar nerve as previously described (4), using 22-gauge steel needle electrodes placed subcutaneously at the wrist. Simultaneous recordings of train-of-four responses, arterial pressure, and heart rate were made on a Grass polygraph (model 7B). Train-of-four monitoring was used in this study as an additional indicator that atracurium is a non-depolarizing relaxant which produced fade of the four responses.

Following a stable base line period of 15 minutes, atracurium was administered as a single rapid (5-second) intravenous bolus. Seven separate dosages were used: 0.06, 0.1, 0.2, 0.3, 0.4, 0.5, and 0.6 mg/kg. The time to maximum neuromuscular blockade was measured. Maximal cardiovascular and neuromuscular changes were obtained in the absence of any stimulation, after which surgery began. Recovery of the initial twitch in the train-of-four to 95% of control twitch was measured after each initial dose. Subsequently, greater than 95% neuromuscular blockade was reestablished with an additional 0.2 mg/kg intravenous bolus of atracurium. When this second dose of atracurium was followed by recovery to a point where the initial twitch in the train-of-four response had recovered to 25% of the control height, the blockade was maintained using incremental doses of atracurium, 0.08 mg/kg, given each time the first twitch of the train-of-four had recovered to 25% of control levels. When the duration of surgery was shorter than anticipated and did not allow for spontaneous recovery of the twitch to control levels, residual blockade was antagonized with a mixture of neostigmine and atropine (0.06 and 0.03 mg/kg, respectively) given as a slow (1-minute) intravenous bolus.

Six patients given 0.06 mg/kg of atracurium were also given 0.2 mg/kg of atracurium 1 hour after the initial dose of atracurium had achieved recovery to control twitch height. (No cumulative effect 1 hour after an initial dose of 0.06 mg/kg of atracurium had been observed in a pilot study [n = 4] in which a second dose of 0.06 mg/kg produced a degree of block not differing significantly from that produced by the first dose.) Thus, the total number of bolus doses given at 0.2 mg/kg were 16 (10 patients from the 0.2 mg/kg dosage group plus an additional six patients from the 0.06 mg/kg dosage group).

Statistical comparisons were considered to show significant differences if $p < 0.05$.

Results

A dose-response curve for neuromuscular blockade was constructed using the log-probit method of Litch-

field and Wilcoxon (5) for doses giving neuromuscular blockade greater than 0% but less than 100% (dose groups 0.06, 0.1, 0.2, and 0.3 mg/kg). These data were then analyzed by computerized linear regressions yielding the straight-line relationship shown in Fig 2. The dose of atracurium derived from this line necessary to achieve 95% neuromuscular blockade (ED_{95}) was 0.20 mg/kg.

The onset time to maximum blockade was dose related, as shown in Table 1. The times to recovery to 95% of control twitch height are also listed in Table 1. Recovery to 95% of control twitch height for the ED_{95} dose (0.2 mg/kg) averaged 44.1 minutes. Administration of 2 times the ED_{95} (0.4 mg/kg) increased the duration of action by 44% to a mean time of 63.5 minutes, whereas 3 times the ED_{95} (0.6 mg/kg) increased the duration of action only 72% to 75.7 minutes.

Using linear regression analysis, no relationship could be found between plasma cholinesterase activity and duration of neuromuscular blockade. Representative graphs for the 0.2 mg/kg and 0.6 mg/kg doses with r values of 0.19 and 0.05, respectively ($p < 0.05$) are shown in Fig 3.

After recovery from the initial dose of atracurium, neuromuscular blockade was reestablished and then maintained with bolus doses of 0.08 mg/kg of atracurium, administered when patients had recovered to approximately 25% of base line twitch height (i.e., suppression was approximately 75%). This maintenance dose increased suppression to approximately 95% of base line twitch height, which then took
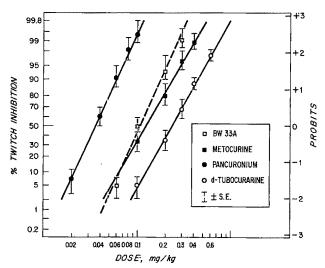
Fig 2. Dose-response curve for atracurium (BW 33A) shown with dose-response curves for d-tubocurarine, pancuronium, and metocurine for comparison (4, 6).

TABLE 1

Neuromuscular and Cardiovascular Effects of Atracurium (BW 33A)*

Drug	Dose	N	Block	Onset	95% recovery	25% to 75% recovery	Blood pressure	Heart rate
	mg/kg		%		min		% control	
BW 33A	0.06	10	4.8 ± 9.0/2.9	6.0 ± 1.8/1.04‡	18.4 ± 0.9/0.6§	—	99.0 ± 4.5/1.4	100.0 ± 2.6/0.8
BW 33A	0.10	10	50.9 ± 32.4/10.2	4.4 ± 0.8/0.3	23.2 ± 6.5/2.2	—	99.5 ± 3.4/1.1	99.2 ± 3.1/1.0
BW 33A	0.20	16	94.1 ± 12.1/3.0	4.0 ± 1.96/0.5	44.1 ± 9.6/2.4	12.3 ± 2.6/0.7‖	96.3 ± 11.3/2.8	100.1 ± 4.7/1.2
BW 33A	0.30	10	99.2 ± 1.5/0.5	2.6 ± 0.9/0.3	48.7 ± 2.6/2.4	10.4 ± 3.1/1.0	98.7 ± 3.5/1.1	99.4 ± 3.7/1.2
BW 33A	0.40	10	99.8 ± 0.4/0.1	1.7 ± 0.6/0.2	63.5 ± 8.5/2.7	11.4 ± 2.3/0.7	99.4 ± 3.0/.95	102.3 ± 3.3/1.0
BW 33A	0.50	10	100.0	1.7 ± 0.5/0.1	67.6 ± 17.2/5.4	11.8 ± 2.8/0.9	86.7 ± 19.3/6.1	105.5 ± 5.3/1.7¶
BW 33A	0.60	10	100.0	1.4 ± 0.5/0.2	75.7 ± 10.0/3.2	12.3 ± 2.4/0.7	79.5 ± 17.9/5.7¶	108.3 ± 12.4/3.9¶
dTc†	0.50	16	98.4	3.9 ± 0.9#	137.0 ± 9.6#**	52.2 ± 42#	\} p < 0.001 for 75% recovery	
BW 33A	0.20	16	94.1	4.0 ± 0.5#	38.6 ± 2.5#**	12.3 ± 0:7*		

* Values are means ± SD/SE.

† From Savarese et al (6) and Ali HH, Savarese JJ, Donlon JV, et al. Comparative study between BW(Y100) (compound AA136) "a new short acting nondepolarizing neuromuscular blocking agent," pancuronium, and d-tubocurarine. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists, 1975, Hollywood, Florida, pp 195–6. Data included for comparison.

‡ N = 3.

§ N = 2.

‖ N = 14.

¶ p = < 0.05 versus control.

Values are means ± SE.

** To 75% recovery.

FIG 3. Plasma cholinesterase activity and duration of action of atracurium (BW 33A) (p > 0.05), 0.2 mg/kg (left) or 0.6 mg/kg (right) doses, demonstrate no correlation. This helps confirm lack of hydrolysis of atracurium by plasma cholinesterase.

FIG 4. Multiple doses of atracurium (BW 33A) show no clinically important cumulative effect. Each time first twitch of train-of-four had recovered to 25% of control twitch height, a fixed increment, 0.08 mg/kg, of atracurium was given. Degree of neuromuscular blockade and time of recovery were essentially unchanged with each dose.

approximately 16 minutes to recover to 25% of base line. With repeated dosing in this manner (one patient received 12 maintenance doses), there was no evidence to suggest that either the amount or the duration of suppression increased with increasing number of doses.

The 25% to 75% recovery times (time for the first twitch in the train-of-four to recover from 25% of control height to 75% of control levels) for the initial and final doses of atracurium in 16 patients receiving at least four successive doses of atracurium were 11.8 ± 1.19/0.5 (SD/SE) minutes and 13.2 ± 2.5/0.6 minutes, respectively. Correlated t-test analysis shows this 1.4-minute difference to be statistically significant (p < 0.025). However, this difference is clinically of

little importance. Patient 62 in this study received 12 successive doses of atracurium and the 25% to 75% recovery times were 10.0 and 12.3 minutes, respectively, for the initial and final doses. In Fig 4 values for a patient who received multiple doses of atracurium are depicted; note the lack of cumulation and that the train-of-four recovery pattern is the same for the first and last doses.

In eight subjects, residual atracurium blockade was readily antagonized with neostigmine (0.06 mg/kg) and atropine (0.03 mg/kg) as shown in Fig 5. The data are shown in Table 2.

In Table 3 reversal of atracurium by neostigmine is compared with reversal of metocurine (4) for a small group of patients with moderate (64% to 85% twitch depression) neuromuscular blockade. Although the

FIG 5. Representative recording show that reversal of atracurium-induced neuromuscular blockade is easily accomplished using neostigmine, 0.06 mg/kg, and atropine, 0.03 mg/kg.

TABLE 2

Antagonism of Atracurium-Induced Neuromuscular Blockade by Intravenous Neostigmine (0.06 mg/kg) and Atropine (0.03 mg/kg)

Twitch height at time of reversal	Time to 95% recovery
% control	min
15	10.5
17	4.5
31	5.0
36	9.0
58	5.5
64	5.5
82	3.5
90	0.75

TABLE 3

Comparative Reversals of Atracurium and Metocurine by Neostigmine*

	No. of patients	% twitch inhibition (range)	Neostigmine dose	Time to 98% of control
			mg/kg	min
BW 33A	4	75.3 (64–85)	0.06	8.2 ± 1.4
Metocurine†	6	79.0 (75–85)	0.05	7.6 ± 0.4

* Atropine, 0.03 mg/kg, was given to each subject along with the neostigmine.
† From Savarese et al (4).

dose of neostigmine is slightly higher in patients given atracurium, the data suggest that atracurium block is readily reversible and requires similar neostigmine dosage as metocurine reversal. The time required for neostigmine antagonism of this degree of blockade by the two drugs also seems comparable (4).

In Table 1 is seen that at all doses up to and including 2 times the ED_{95} (0.4 mg/kg), atracurium produced no statistically significant changes in arterial

pressure or heart rate when paired t-test comparisons were made between control values and maximum changes from control values within the first 10 minutes after the administration of atracurium. At 2.5 (0.5 mg/kg) and 3 times (0.6 mg/kg) the ED_{95} dose, there were mild decreases in arterial pressure to 86.7% and 79.5% of control levels, respectively, and mild increases in heart rate to 105.5% and 108.3% of control levels, respectively (Fig 6). Changes in arterial pressure were statistically significant only at the 0.6 mg/kg dose ($p < 0.05$). Heart rate changes were significant for both the 0.5 mg/kg and 0.6 mg/kg doses ($p < 0.05$). These changes were of short duration, the maximal effect occurring 1 to 1.5 minutes after drug injection with a total duration of less than 5 minutes. These cardiovascular changes were associated with slight facial flushing.

Discussion
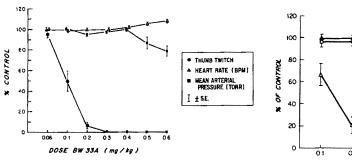
This study has shown atracurium to be a potent non-depolarizing blocking agent. Atracurium is 2.5 times more potent than d-tubocurarine, approximately 50% more potent than metocurine, and one fourth to one third as potent as pancuronium. At doses up to the approximate ED_{95} and ED_{99} (0.2 and 0.3 mg/kg, respectively), the onset of action of atracurium is comparable to other clinically used non-depolarizing relaxants (4, 6) and is dose related.¶ For example, by doubling the dose from 0.2 to 0.4 mg/kg, onset to maximum blockade was shortened from 4.0 to 1.7 minutes, although the total duration of effect increased by only approximately 19 minutes or 44% (Table 1). The time to and ease of intubation were not evaluated in the present study. Payne and Hughes (3), however, showed that in six patients receiving 0.3 mg/kg of atracurium, intubation was easily accomplished within 1.5 to 2.0 minutes, and in six patients given 0.6 mg/kg of atracurium intubation was accomplished within 1 minute. In our study, the onset times to maximum block at 0.3 and 0.6 mg/kg of atracurium were 2.6 and 1.4 minutes, respectively. These onset times suggest that in this dose range of atracurium, intubation might be accomplished within 2 to 3 minutes, or less.
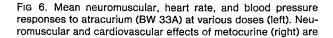
The duration of action of atracurium is relatively short compared with other non-depolarizing agents,
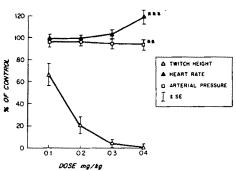
¶ Ali HH, Savarese JJ, Donlon JV, et al. Comparative study between BW(Y100) (compound AA136) "a new short acting non-depolarizing neuromuscular blocking agent," pancuronium, and d-tubocurarine. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists, Oct 11–15, 1975, Chicago, Illinois, pp 195–6.

FIG 6. Mean neuromuscular, heart rate, and blood pressure responses to atracurium (BW 33A) at various doses (left). Neuromuscular and cardiovascular effects of metocurine (right) are shown for comparison (4). At equipotent neuromuscular blocking doses, atracurium produces less cardiovascular effects than does metocurine.

lasting approximately one third as long as currently used non-depolarizing drugs. In addition, the consistent pattern of recovery observed after repeated doses of atracurium for maintenance of neuromuscular blockade indicates that it is essentially a noncumulative relaxant.

In those few instances in which antagonism of residual block was necessary, it was easily accomplished by administration of neostigmine and atropine. The speed of reversal was comparable to reversal of metocurine-induced blockade at a similar degree of blockade.

The intermediate duration of action and the lack of cumulative effects of atracurium are probably due to its unique manner of decomposition and metabolism. The molecule was deliberately structured to decompose spontaneously at physiologic pH and normal body temperature by a base-catalyzed reaction termed the Hofmann elimination (1) (Fig 1). In this reaction, the protons on the alpha-carbon atoms (carbon atoms located adjacent to the carbonyl carbon atoms) are acidic. At physiologic pH, a proton can dissociate from the alpha-carbon, leaving an electronegative charge. This allows cleavage of the bond between the beta-carbon (at the end of the intermediate chain of atracurium) and the positively charged nitrogen atom. This cleavage yields an inactive tertiary amine and a diolefin diester as shown in Fig 1. Experiments in animals (Hughes and Chapple [2]), in which the pH was increased from 7.31 to 7.63 by hyperventilation, yielded a significant reduction in the amount and duration of block by atracurium, confirming by inference in vivo occurrence of the Hofmann elimination as this is a base-catalyzed reaction.

An alternate metabolic pathway is also shown in Fig 1. This is believed to be enzymatic hydrolysis of the ester yielding two monoquaternary carboxylic acids and a dialcohol. This enzymatic hydrolysis is

probably not dependent on plasma cholinesterase for the following reasons: atracurium is not a choline ester; in vitro hydrolysis in normal human serum and in plasma cholinesterase-deficient human serum is not different (3); and, in the present study, there is no correlation between duration of action of atracurium and plasma cholinesterase activity. It is also interesting to note that in the study of Payne and Hughes (3) in humans, decreasing plasma pH from 7.50 to 7.35 did not increase the duration of action of atracurium, suggesting that the enzymatic ester hydrolysis is functioning more efficiently at the lower pH. Thus, the relative roles of the enzymatic hydrolysis and Hofmann elimination in man have yet to be determined. It may be that each is important, depending on the extracellular pH.

Hughes and Chapple (2) also investigated the role of the liver and kidneys in the elimination of atracurium in cats. The doses of atracurium necessary to produce 50% blockade when given via the jugular vein or the hepatic vein were not significantly different. Further, the ED_{50} was not significantly changed following renal pedicle ligation, nor was the time to recovery significantly prolonged. Thus, in animals neither uptake or metabolism by the liver nor elimination by the kidneys appears to be absolutely necessary for recovery from the effects of atracurium. Further studies in man are needed to confirm these initial findings in animals.

The cardiovascular responses to atracurium as a function of degree of neuromuscular blockade in this study were found, under similar anesthetic conditions, to be more favorable than those associated with metocurine (4), the relaxant currently acknowledged to have the least effect on the cardiovascular system. Payne and Hughes (3) found no significant change in either arterial pressure or heart rate at doses up to 0.6 mg/kg (3 times the ED_{95}), whereas in the present

study, we found slight decreases in arterial pressures and slight increases in heart rate at doses greater than 0.4 mg/kg. The decreases in arterial pressure and the increase in heart rate noted in the present study peaked at 1 to 1.5 minutes, had disappeared within 5 minutes, and were often associated with slight facial flushing. The latter may be due to a relatively weak histamine-releasing property.

The following, in summary, can be said of atracurium: (a) It is a potent non-depolarizing neuromuscular blocking agent with approximately one third the duration of action of currently used non-depolarizing relaxants. (b) It has a rapid onset of action, especially at 2 times the ED_{95} dosage, which suggests that intubation may be accomplished within approximately 2 to 3 minutes at this dosage. Further clinical studies are needed to confirm this initial clinical impression. (c) It has less cardiovascular side effects than metocurine at comparable neuromuscular blocking doses, and has little or no cardiovascular effects at up to 2 times the ED_{95}. By comparison (Fig 4), metocurine begins to show signs of histamine release at approximately 1.3 times the ED_{95}. (d) It does not show any clinically important cumulative effects. (e) Initial metabolic studies suggest that atracurium undergoes a unique decomposition in plasma to inactive metabolites via the Hofmann elimination (2, 3). It may also undergo ester hydrolysis by an enzymatic pathway

that does not involve plasma cholinesterase (3). (f) In animals, initial work suggests that atracurium is not dependent on liver metabolism or renal elimination for termination of its action (2). (g) Its action is readily antagonized by neostigmine.

For these reasons, atracurium is an intermediate-duration non-depolarizing neuromuscular blocking agent of significant clinical potential and should undergo more extensive clinical trials.

ACKNOWLEDGMENTS

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Neuromuscular Effects of Atracurium in Man

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KATZ, R. L., STIRT, J., MURRAY, A. L., AND LEE, C.: Neuromuscular effects of atracurium in man. Anesth Analg 1982;61:730-4.

The neuromuscular effects of atracurium were studied in 25 A.S.A. class I or II patients anesthetized by a N_2O-O_2 narcotic technique. In five patients incremental doses of 0.05 to 0.1 mg/kg of atracurium were given intravenously every 3 minutes until approximately 95% depression of the evoked electromyographic (EMG) response of the adductor policus muscle was produced. This required 0.25 to 0.35 mg/kg of atracurium. The duration of block (return to 95% of control) was 25 to 50 minutes. In addition, four groups of five patients each received 0.15, 0.25, 0.375, or 0.6 mg/kg of atracurium. The block produced by 0.15 mg/kg was 10% to 92% and lasted 8 to 55 minutes. The block produced by 0.25, 0.375, and 0.6 mg/kg was 95% or greater with a duration of action of 30 to 68 minutes, 52 to 70 minutes, and 65 to 95 minutes, respectively. Tracheal intubation was easily carried out in all patients in whom there was a block of 90% or greater. The block could be antagonized by the common clinical combination of atropine and neostigmine. Changes in heart rate and blood pressure following atracurium were less than 5%.

Key Words: NEUROMUSCULAR RELAXANTS: atracurium.

ATRACURIUM (BW 33A) is one of a new series of neuromuscular blocking agents developed by Stenlake (1). Its structural formula is shown in Fig 1. In animal studies carried out by Hughes and Chapple (2), atracurium was shown to be a non-depolarizing neuromuscular blocking agent with little or no cardiovascular effect. Because of the promising results in animals, Payne and Hughes (3) in England studied atracurium in anesthetized patients and found the drug to possess many desirable properties. Recently, this drug has become available for clinical investigation in the United States. In this paper, we report the neuromuscular effects of atracurium in anesthetized patients.

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Methods

Twenty-five patients undergoing surgery, who were between 18 and 60 years old, weighing 48 to 96 kg, A.S.A. class I or II, and free of neuromuscular disease, were studied. Informed patient consent was obtained and the study was approved by the University of California, Los Angeles Human Subject Protection Committee. Most patients received meperidine, 25 to 75 mg, intramuscularly (IM) or intravenously (IV) (18 patients) and/or diazepam, 2.5 to 10 mg IV (17 patients) before induction of anesthesia, which was carried out with thiopental, 1 to 6 mg/kg. Anesthesia was maintained with nitrous oxide-oxygen (60%/40%) supplemented with intravenous narcotics or thiopental. No muscle relaxants other than atracurium were given. In the 20 patients in whom the trachea was intubated because of clinical indications, intubation was done after atracurium was given. After the muscle relaxant was given, ventilation was controlled to maintain normal acid-base balance. Blood pressure and heart rate were monitored by the Riva Rocci technique and from the electrocardiogram. The monitoring interval for blood pressure was 1 minute for the time period 3 minutes before atracurium injection to 5 minutes after injection. At other times, the monitoring interval was 1 to 5 minutes as clinically indicated. Heart rate was continuously monitored.

Neuromuscular transmission was monitored as previously described (4). Briefly, the ulnar nerve was stimulated at the wrist via 25-gauge needles subcutaneously placed. Supramaximal stimuli of 0.3 msec duration were applied at a frequency of 0.15 Hz. The electromyographic (EMG) activity of the adductor pollicus muscle was continuously recorded.

In the first five patients, a dose of 0.05 to 0.1 mg/kg was injected intravenously every 3 minutes in an attempt to produce a 95% neuromuscular block. The next 20 patients, divided into four groups of five patients each, were given intravenous doses of 0.15, 0.25, 0.375, or 0.6 mg/kg of atracurium. When clinically possible, recovery to 95% of control levels was measured. In some patients, additional doses of atracurium were given as clinically required, and the effects of the drug were antagonized with neostigmine, 2.5 mg, following administration of atropine, 1 mg.

Results

The neuromuscular effects of cumulative doses given the first five patients are listed in Table 1. Note the variability of responses to the three doses that all five patients received (Table 1, A). Doses of 0.25 to 0.35 mg/kg produced blocks of 90% to 100% which lasted 26 to 50 minutes (Table 1, B). In one patient, antagonism of the block was required because of a briefer duration of surgery than anticipated. An example of the cumulative dose response is shown in Fig 2.

In Table 2 are shown the percent block, onset time, and duration to 95% recovery of 0.15, 0.25, 0.375, and

TABLE 1

Cumulative Doses of Atracurium

A. Percent of block produced by cumulative doses:			B. Cumulative doses required to produce approximately 95% block			
0.1 mg/ kg	0.2 mg/ kg	0.25 mg/ kg	Dose	Block	Onset*	Dura- tion† to 95% re- covery
			mg/kg	%		min
0	15	25	0.25	90	10	38
0	25	62	0.25	92	11	50
0	50	82	0.30	92	12	26
8	59	90	0.35	95	17	48
12	81	92	0.35	100	14	—‡
X̄ = 4	X̄ = 46	X̄ = 70				

* Onset, time from initial dose to peak effect.

† Duration, time from peak effect to 95% recovery.

‡ Block was antagonized before duration could be measured.
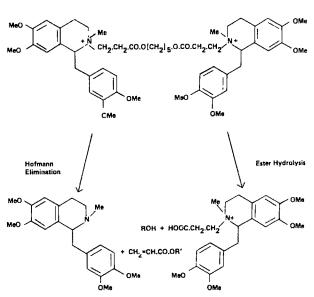
FIG 1. Structural formula of atracurium and its metabolic pathways.

I₁ I₂ I₃ I₄   5 min

1,2 = 0.1mg/kg BW33A
3,4 = 0.05mg/kg BW33A
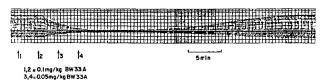
FIG 2. Electromyographic effects of four doses of atracurium to a total of 0.3 mg/kg. Block was profound but there was rapid recovery.

0.6 mg/kg of atracurium given as a single bolus. An example of the variability of response is shown in Fig 3. A comparison of the effect of 0.25 mg/kg of atracurium when given by the cumulative technique as compared with a single bolus can be obtained by comparing Table 1, A and Table 2. Note that a greater effect was obtained when bolus doses were given. With the cumulative technique, the blocks varied from 25% to 92%, whereas with the bolus technique, the blocks varied from 95% to 100%.

In five of the 25 patients, it was necessary to antagonize the neuromuscular block with neostigmine preceded by atropine. The percent block at the time of antagonism varied from 10% to 90%. Antagonism to 95% of control response required 10 minutes or less. An example of antagonism of the atracurium neuromuscular block is shown in Fig 4.

The heart rate and blood pressure in the 5 minutes following atracurium injection differed less than 5% from the 3-minute time period before atracurium injection. Systolic pressure was 82 to 140 (mean 110) torr, diastolic pressure 50 to 90 (mean 68) torr, and heart rate 56 to 105 (mean 72) beats per minute.

TABLE 2
Neuromuscular Effects of Atracurium*

% of block at various doses	Onset	Duration to 95% recovery
	min	
0.15 mg/kg		
10	8	8
73	8	26
77	9	30
80	9	32
92	6	55
0.25 mg/kg		
95	5.5	30
95	7	34
97	3.5	68
100	4	—
100	7	—
0.375 mg/kg		
95	10	56
100	4	54
100	4.5	70
100	5	59
100	6.5	52
0.6 mg/kg		
100	2.5	70
100	2.5	95
100	3	70
100	4	65
100	4	67

* Onset time. from injection of drug to peak effect; duration, from time of peak effect to 95% recovery.
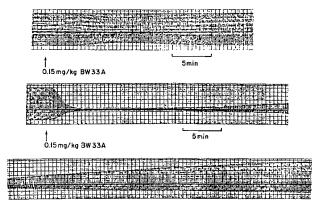
Fig 3. Electromyographic effects of 0.15 mg/kg of atracurium. Note minimal effect of this dose in one patient (top). Greater magnitude of block and longer duration of action are shown in another patient (middle and bottom).

Endotracheal intubation was carried out in 20 of 25 patients. The speed with which intubation could be carried out was not determined as we wished to determine the cardiovascular effects of atracurium in the first 5 minutes following atracurium injection in the absence of any stimulation. Once this 5-minute period had passed, all patients with a block of 90% or
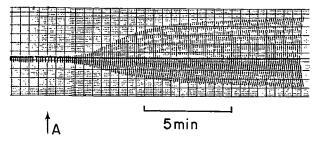
Fig 4. Antagnoism of atracurium neuromuscular block. Arrow A indicates point at which atropine, 1 mg, and neostigmine, 2.5 mg, were given. Note antagonism of block.

greater could be intubated with ease. In patients given 0.375 or 0.6 mg/kg, conditions were excellent, with the cords widely adducted and no response to either intratracheal spray of 4% lidocaine or to intubation. Of the 10 patients given either 0.25 mg/kg as a bolus or cumulative doses of 0.25 to 0.35 mg/kg of atracurium, the cords were adducted in all 10 and there was no response to topical spray or intubation in seven. In the remaining three patients, a barely perceptible cough or coughs of 2 to 3 seconds' duration was observed. Patients who received 0.15 mg/kg of atracurium were not intubated.

Discussion

Following the development of atracurium by Stenlake (1), the drug was studied by Hughes and Chapple (2) in animals and by Payne and Hughes in man (3). The former investigators, using the isolated check biventer-cervices preparation, observed that atracurium produced a competitive or non-depolarizing-type block without producing an initial contracture (seen with depolarizing agents). The block could be antagonized by physostigmine or edrophonium. Additional studies in the cat, dog, and rhesus monkey confirmed that atracurium was a non-depolarizing neuromuscular blocking agent that could be antagonized by edrophonium and neostigmine.

A comparison of doses producing twitch depression with doses inhibiting vagal nerve stimulation-induced bradycardia showed that atracurium caused appreciable vagal blockade only at doses 16 times greater than the full neuromuscular paralyzing dose. There was also a large difference between the neuromuscular paralyzing dose and the dose required to inhibit the hypertensive response to bilateral common carotid artery occlusion or the contraction of the nictitating membrane induced by sympathetic stimulation. Hughes and Chapple (2) also showed a wide separation between doses causing neuromuscular effects

and those causing changes in heart rate or blood pressure. For example, in the cat, the doses that produced a 40% decrease in blood pressure and a 5% decrease in heart rate were 16 times greater than the dose required to produce 100% depression of twitch response. Similar wide separation of neuromuscular and cardiovascular effective doses were observed in the rhesus monkey and dog. Additional hemodynamic studies in the dog measuring phasic aortic flow, cardiac output, or peripheral resistance again revealed a wide separation between neuromuscular-effective and cardiovascular-effective doses with larger doses required to produce cardiovascular effects. Evidence of histamine release was found only after administration of doses of atracurium 8 times the neuromuscular paralyzing dose.

Hughes and Chapple (2) studied the elimination of atracurium. They found that neither the liver nor the kidney played a major role in metabolism or elimination of atracurium. They further observed that atracurium was broken down by Hofmann elimination (Fig 1) and that in vitro this nonenzymatic decomposition increased at least 3-fold when pH was increased from 6.9 to 7.6. At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH. Another likely metabolic pathway is via enzymatic ester hydrolysis (Fig 1).

Following these promising results in animals, Payne and Hughes (3) studied atracurium in man. They studied doses ranging from 0.05 to 0.6 mg/kg. In patients under balanced anesthesia a dose of 0.2 mg/kg produced 74% depression of the mechanically recorded twitch, whereas 0.3 mg/kg produced 100% block in most patients. Spontaneous recovery from atracurium was faster than with dimethyl tubocurarine, tubocurarine, pancuronium, or fazadinium. The atracurium block could be antagonized by neostigmine. Endotracheal intubation in patients receiving thiopental followed by atracurium could be carried out within 2 minutes after a dose of 0.3 mg/kg of atracurium and within 1 minute in patients given 0.6 mg/kg. Minimal cumulative effect was seen with atracurium. Doses of 0.2, 0.3, and 0.6 mg/kg of atracurium did not change arterial pressure or heart rate.

In the present study, the response to atracurium was found to vary from patient to patient. This was not a surprising finding as we have previously shown that for both d-tubocurarine (5) and pancuronium (6) the responses of patients differ markedly. In the present study, a dose of 0.15 mg/kg could produce as little as a 10% block lasting 8 minutes or a 92% block lasting 55 minutes. We also observed that, as we

previously reported for pancuronium (6), knowing the percent block did not enable accurate prediction of the duration of action. Patients with comparable blocks produced by atracurium had durations of blocks that differed by as much as 100%.

We also found that atracurium doses of 0.25 mg/kg or larger produced conditions suitable for endotracheal intubation. It is not possible to state how rapidly intubation could be carried out as we did not attempt intubation until 5 minutes after the drug was given in order to determine heart rate and blood pressure effects of atracurium in the absence of any stimulation. Of the patients who received 0.25 or 0.375 mg/kg of atracurium in a bolus or 0.25 to 0.35 mg/kg by cumulative dose and were then intubated, spontaneous recovery occurred in 30 to 59 minutes in 11 patients and in 65 and 70 minutes in two other patients. In the remaining two patients, clinical circumstances did not permit determination of recovery time. A drug that permits endotracheal intubation and that wears off in 1 hour or less is certain to be of great clinical value. Even with the largest dose of atracurium studied (0.6 mg/kg), spontaneous recovery occurred in 1 to 1.5 hours. In addition, in the present study and in other studies in progress, the atracurium block was easily antagonized by neostigmine after periods as short as 20 minutes. Although we did not study the rapidity with which patients could be intubated after atracurium, we are surprised that Payne and Hughes (3) were able to intubate patients within 1 minute after 0.6 mg/kg of atracurium or within 2 minutes after 0.3 mg/kg. Based on the times of onset of block in the present study and our past experience with pancuronium, it is our guess that intubation could have been carried out within 2 minutes after a dose of 0.6 mg/kg and within 3 minutes after a dose of 0.3 mg/kg.

It is not possible to compare the results of our study with that of Payne and Hughes (3) because of major differences in experimental design. Most of their patients received halothane to facilitate intubation and it was then discontinued in some, but not all, patients. They also measured tetanic as well as twitch responses, the former being more sensitive in terms of speed of onset of depression but giving a longer apparent duration of block. In addition, they studied mechanical responses, which measure not only neuromuscular transmission but also any possible muscle effects, whereas we measured electromyographic responses which only assess neuromuscular transmission. In a previous study of d-tubocurarine (7), we found that the EMG twitch depression of the adductor

pollicus was usually 10% to 15% less than the simultaneously recorded mechanical twitch produced by the same muscle. We do not know whether this is true for atracurium, although this is currently under investigation.

An interesting observation of the present study is that the dose required to produce a given percent of block depends on whether the dose is given by single bolus or in a cumulative manner. Under the conditions of this study in which doses were given 3 minutes apart, lesser effect was seen with 0.25 mg/kg given by the cumulative method than with a bolus dose of 0.25 mg/kg of atracurium. A similar conclusion can be drawn when comparing the effect of 0.2 mg/kg given by the cumulative technique, which produced a mean block of 46%, whereas a single dose of 0.15 mg/kg produced a mean block of 67%. Thus, in future comparisons of the work of different investigators, the technique of construction of dose-response curves (whether cumulative or bolus technique) must be taken into account.

Having just pointed out the many differences between our study and that of Payne and Hughes, both studies nevertheless agree that: (a) atracurium is capable of providing conditions suitable for endotracheal intubation without producing cardiovascular effects, (b) intubating doses of atracurium have a shorter duration of action than other currently available non-depolarizing agents, and (c) the neuromuscular block produced by atracurium is readily antagonized by neostigmine.

Because we are simultaneously studying ORG NC 45, we would mention that at the present stage of our studies with both drugs, we feel that if the drugs were appropriately diluted and given to us in unlabeled syringes and then administered with the aid of a peripheral nerve stimulator, we would be unable to distinguish between ORG NC 45 and atracurium in terms of onset of action, magnitude of effect, duration of action, or cardiovascular effects.

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Comparison of Venous Admixture during High-Frequency Ventilation and Conventional Ventilation in Oleic Acid-Induced Pulmonary Edema in Dogs

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SCHUSTER, D. P., SNYDER, J. V., AND KLAIN, M.: Comparison of venous admixture during high-frequency ventilation and conventional ventilation in oleic acid-induced pulmonary edema in dogs. Anesth Analg 1982;61:735–40.

High-frequency jet ventilation (HFJV) was compared with conventional ventilation during oleic acid-induced pulmonary edema in dogs. HFJV, when combined with positive end-expiratory pressure (PEEP), returned arterial P_{O_2} (Pa_{O_2}) and venous admixture to preoleic acid levels, even with tidal volumes as low as 4.8 ml/kg and rates of 300 min^{-1}. When HFJV was compared with conventional (low-frequency, high tidal volume) ventilation at the same $F_{I_{O_2}}$ and level of PEEP, Pa_{O_2} was lower and venous admixture higher with HFJV. However, venous admixture was lower with HFJV when comparisons were made at the same peak airway pressure, because of a higher level of PEEP compared with conventional ventilation. At each level of PEEP, cardiac and stroke indices were not different between the two methods of ventilation. The ability to eliminate CO_2 with lower peak airway pressures or to increase PEEP without further increases in peak airway pressure are the primary advantages of HFJV during severe lung injury. Oxygenation is as efficient during HFJV as during conventional ventilation in this model of pulmonary edema when comparisons are made at the same peak airway pressure, but less efficient at the same PEEP.

Key Words: VENTILATION: high frequency; LUNG: venous admixture.

C URRENT techniques of mechanical ventilation during respiratory insufficiency provide adequate CO_2 elimination and improved arterial oxygenation in the majority of cases. Recently, however, a number of investigators (1–4), using a variety of techniques, have suggested on the basis of a limited patient experience that high-frequency ventilation may improve arterial oxygenation at lower airway pressures. We report the use of one form of high-frequency ventilation, namely, high-frequency jet ventilation (HFJV) (5) in an experimental model of pulmonary edema induced by oleic acid. In these experiments, we attempt to define more clearly the potential utility of HFJV and to elucidate the mechanisms by which this technique might improve arterial oxygenation, by making comparisons of gas exchange and hemodynamics at comparable airway pressures and inspired oxygen concentrations.

Methods

Eighteen mongrel dogs of either sex, weighing 10 to 20 kg each, were anesthetized with 25 to 30 mg/kg of sodium thiopental. Additional drug was given as needed to suppress spontaneous breathing. Following tracheal intubation with a 9.0-mm i.d. endotracheal tube, the dogs were ventilated initially with a Harvard pump respirator at a tidal volume of 12 to 15 ml/kg (mean 14.0). The rate was adjusted to bring arterial CO_2 tension (Pa_{CO_2}) and pH into the normal range. This ventilation pattern is referred to as conventional ventilation (CV). Intravenous fluids and medications were given via a peripheral vein. Arterial pressure was measured via PE 90 tubing inserted into the femoral artery. A thermistor-tipped pulmonary arterial catheter (Edwards Laboratories #5 French) was positioned via the femoral vein. Correct position of the catheter was assumed if the pressure tracings changed from those typical of the pulmonary artery to "wedge"-type pressures after introduction of 0.8 ml of air into the balloon at the catheter tip. Airway pressure (AWP) was measured at the tip of the tra-

cheal tube via PE 90 tubing. All catheters were saline filled and connected to Statham P23-ID pressure transducers. Vascular catheters were leveled at a height of 5 cm above the operating table. The airway pressure transducer was set at a level such that during expiration, in the control state, airway pressure decreased to zero. All pressures and a lead II electrocardiogram were recorded with a Grass model 7D polygraph.

Cardiac output was measured in triplicate, using the thermodilution technique (Edwards Laboratories model 9510-A computer) with injection of 3 ml of 5% dextrose in water at a temperature of 0 to 3°C. Arterial and pulmonary arterial blood gas tensions and pH were measured using an Instrumentation Laboratory 813 blood gas analyzer. Venous admixture ($\dot{Q}va/\dot{Q}t$) was calculated with a computer program that utilized the standard form for the shunt equation, after correcting for temperature, pH, and CO_2 and using a value for P_{50} of 26.6 torr. Heart and respiratory rates were measured from the recorded tracings and cardiac and stroke indices computed using a formula based on body surface area (BSA) (6): BSA = 0.12 (weight, kg)$^{2/3}$. Exhaled minute volume was measured with a Bourns LS 75 ventilation monitor and tidal volume was calculated as minute volume divided by respiratory frequency. Mean airway pressure was calculated by digitizing the analog wave form of airway pressure over several respiratory cycles with a Graf pen sonic-digitizer, integrating the data with a Wang 600 computer, and dividing by time.

HFJV was delivered using the apparatus shown schematically in Fig 1. A 50% oxygen-nitrogen mixture of gases from a cylinder was delivered via a Y-connector to the ventilator (5, 7) and to a 3-L reservoir bag via a flowmeter. The flowmeter, in turn, was attached via appropriate one-way valves to the endotracheal tube. Thus, the high-velocity jet and any entrained gas were at the same O_2 concentration (F_{IO_2}). The driving pressure (the major determinant of minute volume) for the gases into the ventilator was adjusted with a reducing valve. Inspiratory and expiratory times were set separately using controls on the ventilator. Thus, tidal volume, inspiratory-to-expiratory time (I:E) ratio, and ventilatory frequency could be adjusted. Positive end-expiratory pressure (PEEP) was obtained by placing a combination of Boehringer and magnetic PEEP valves into the expiratory line; PEEP was measured at the tip of the endotracheal tube.

After instrumentation, control data were recorded followed by administration of 0.1 ml/kg of oleic acid
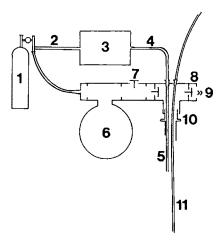
Fig 1. Schematic drawing of apparatus used to provide high-frequency jet ventilation: 1, 50% O_2/N_2 gas cylinder; 2, high pressure tubing; 3, fluidic-controlled high-frequency ventilator; 4, noncompliant small bore tubing; 5, 14-gauge, 10-cm length "jet" cannula; 6, 3-L reservoir bag; 7, low-resistance "pop-off" valve; 8, non-rebreathing T-piece; 9, exhalation port for applying PEEP and measuring exhaled minute volume; 10, endotracheal tube connection; 11, PE-90 tubing for measuring airway pressure.

over 3 to 5 minutes into the right atrial port of the pulmonary arterial catheter (8). After 1.5 hours, the animals were divided into two groups and treated as described below.

"Equal PEEP" Group (n = 10)

In this group, comparisons of CV and HFJV were made at 0, 6, and 10 torr of PEEP. Each animal served as his own control and data were collected 45 to 60 minutes after each ventilator change. At each level of PEEP, CV or HFJV was used in random order. During the initial application of PEEP, normal saline (15 ml/kg) was administered over 30 minutes. Wedge pressure never exceeded 15 torr. In six animals, driving pressure was 40 psi and rate 300 min^{-1}; in four, the driving pressure was 10 to 30 psi and the rate was 100 min^{-1}. Inspiratory-to-expiratory time ratios between 1:2 and 1:1 were used. In general, the higher driving pressures resulted in greater minute volumes and therefore lower Pa_{CO_2} levels. With this exception, no systematic differences in gas exchange were noted for the various ventilator settings, and therefore the group is considered as a whole.

"Equal Peak AWP" Group (n = 8)

In contrast to the above, ventilation modes in these animals were used in a prescribed order. As above, measurements were made 45 to 60 minutes after each change in ventilation. The sequence was CV (0 torr

TABLE 1

Comparisons at Same PEEP and F_{IO_2} of High-Frequency Jet Ventilation (HFJV) and Conventional Ventilation (CV)*

	PEEP	Peak AWP	Mean AWP	Pa_{CO_2}	Pa_{O_2}	$\dot{Q}va/\dot{Q}t$	$P\bar{v}_{O_2}$	CI	SI
				torr		*%*	*torr*	*L/min/m²*	*ml/min/m²*
Control									
CV (n = 10)	0	7.5 ± 1.4	1.9 ± 0.7	39.2 ± 6.1	213.8 ± 3.8	18.7 ± 4.8	66.5 ± 11.7	4.87 ± 1.4	24.8 ± 7.7
After oleic acid									
CV (n = 9)	0	13.0 ± 3.2 ‡	2.8 ± 0.9	38.6 ± 6.6 ‡	89.1 ± 24.6¶	35.1 ± 11.5 ‡	49.8 ± 9.6 †	3.36 ± 1.0	23.7 ± 9.5
HFJV (n = 9)	0	10.0 ± 3.2 ‡	4.0 ± 1.5	25.1 ± 10.0 ‡	66.6 ± 20.4‖	44.3 ± 10.5 ‡	41.8 ± 1.6 †	3.54 ± 1.2	19.7 ± 6.8
CV (n = 10)	6	17.2 ± 3.5 ¶	8.8 ± 1.5	35.6 ± 3.6 §	146.8 ± 45.6‖	21.0 ± 12.4 §	51.8 ± 13.8‖	2.58 ± 1.1	16.1 ± 7.8
HFJV (n = 10)	6	13.1 ± 3.2 ¶	9.4 ± 1.6	27.4 ± 8.8 §	105.0 ± 47.2‖	28.8 ± 12.6 §	43.9 ± 11.5‖	2.74 ± 1.0	14.6 ± 6.2
CV (n = 5)	10	21.2 ± 1.1 †	13.2 ± 1.0	42.7 ± 8.1	203.6 ± 71.5†	12.8 ± 4.0 †	61.7 ± 26.6	1.88 ± 0.6	10.7 ± 4.6
HFJV (n = 5)	10	17.4 ± 2.6 †	13.6 ± 1.6	34.2 ± 8.2	165.8 ± 73.6†	17.6 ± 7.2 †	55.4 ± 19.7	2.24 ± 0.8	12.0 ± 5.8

* Values are means ± SD. All data obtained at F_{IO_2} of 0.5. Abbreviations used are: PEEP, positive end-expiratory pressure; AWP, airway pressure; $\dot{Q}va/\dot{Q}t$, venous admixture as percentage of total cardiac output; $P\bar{v}_{O_2}$, mixed venous oxygen tension; CI, cardiac index; SI, stroke index. Statistical analysis is of paired comparisons between ventilator types at the same level of PEEP.
† $p < 0.05$.
‡ $p < 0.025$.
§ $p < 0.01$.
‖ $p < 0.005$.
¶ $p < 0.001$.

PEEP), CV (8 torr PEEP), and HFJV (12 torr PEEP). In this way, CV (8 torr PEEP) was compared with HFJV (12 torr PEEP) at the same peak airway pressure.

Statistics

Statistical differences between CV and HFJV at the various levels of PEEP were assessed using Student's t-test for paired data.

Results

Equal PEEP Group

In these experiments, the effects of HFJV and CV are compared at the same levels of PEEP in the same animals. The results are presented in Table 1. Tidal volume during CV averaged 14.0 ± 2.7 ml/kg, whereas it was 7.2 ± 2.3 ml/kg during HFJV. These lower tidal volumes resulted in consistently lower peak airway pressures during HFJV at any given level of PEEP. In contrast, mean airway pressure (AWP) was not significantly different during HFJV at the same PEEP. Airway pressures in one animal during both modes of ventilation at 6 torr of PEEP are superimposed on one another in Fig 2.

Arterial P_{O_2} was consistently lower and $\dot{Q}va/\dot{Q}t$ higher during HFJV when compared with CV at similar levels of PEEP. In both systems, however, Pa_{O_2} and $\dot{Q}va/\dot{Q}t$ improved in direct proportion to the increases in PEEP. At 10 torr of PEEP, $\dot{Q}va/\dot{Q}t$ had decreased to or below control levels with both systems.

Cardiac and stroke indices were not different in the
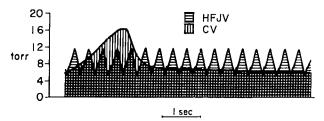
FIG 2. Airway pressures (AWPs) (on ordinate) during HFJV are superimposed on wave form of AWP during single cycle of conventional ventilation (CV). AWPs were traced directly from chart recordings. Chart speed was 25 mm/sec. Horizontal lines indicate areas under AWP wave forms used to compute mean AWP during HFJV. Vertical lines indicate an analogous area for CV. Mean AWP during HFJV in this case was 8.7 torr; during CV, 7.3 torr.

two systems, although both decreased as PEEP increased. Arterial blood pressure did not change significantly when HFJV was instituted. In contrast to these findings, the mixed venous P_{V_2} ($P\bar{v}_{O_2}$) was lower during HFJV at all levels of PEEP, although not significantly at 10 torr of PEEP. Arterial P_{CO_2} was also consistently lower between ventilation modes at each level of PEEP (but again, not significantly at 10 torr of PEEP). This discrepancy occurred because high driving pressures (and, therefore, minute ventilation) were used more frequently in those groups ventilated at the lower levels of PEEP. However, of 24 comparisons made at all levels of PEEP, eight were made with arterial P_{CO_2} within 5 torr of each other. In seven of these eight cases, the directional changes in Pa_{O_2} and $\dot{Q}va/\dot{Q}t$ were the same as for the group as a whole, and in the eighth case there was no difference in either direction.

TABLE 2

Comparison of High-Frequency Jet Ventilation (HFJV) and Conventional Ventilation (CV) at Same Peak Airway Pressure but Different Levels of PEEP (n = 8)*

	PEEP	Peak AWP	Mean AWP	Pa_{CO_2}	Pa_{O_2}	$\dot{Q}va/\dot{Q}t$	$P\bar{v}_{O_2}$	CI	SI
			torr			%	torr	L/min/m²	ml/min/m²
Control									
CV	0	7.6 ± 1.4	1.8 ± 8.2	38.6 ± 8.2	233.1 ± 17.9	14.0 ± 5.2	60.6 ± 13.0	4.96 ± 1.97	25.0 ± 9.8
After oleic acid									
CV	0	10.4 ± 3.4‡	2.5 ± 0.9||	38.0 ± 5.9	90.8 ± 39.9¶	33.1 ± 15.4‡	43.0 ± 11.2§	3.16 ± 1.07‡	20.1 ± 5.6†
CV	8	19.2 ± 2.6¶	11.0 ± 1.1	39.2 ± 6.9	174.8 ± 55.0||	12.2 ± 4.9||	46.4 ± 11.8	2.42 ± 1.11‡	14.6 ± 7.7||
HFJV	12	19.8 ± 2.4	14.7 ± 0.8¶	40.7 ± 5.0	204.2 ± 42.4†	7.7 ± 2.2§	42.6 ± 10.0	2.12 ± 1.06†	10.7 ± 5.9§

* Values are means ± SD. All data obtained at $F_{I_{O_2}}$ of 0.5. Abbreviations and symbols of statistical significance are defined in Table 1 footnotes. Statistical analysis indicates comparison of each group with ventilation at previous level of PEEP.

Same Peak AWP Group

To see whether we could avoid the consistent decrease in Pa_{O_2} during HFJV, we took advantage of the smaller tidal volumes used during HFJV. To do this, we increased PEEP in this series of animals with each change from the Harvard pump respirator to HFJV; but adjusted driving pressure and rate so that peak airway pressure did not exceed that obtained during CV (with its larger tidal volumes) at the lower PEEP. These results are presented in Table 2. The data show that when PEEP was increased from 8 to 12 torr in changing to HFJV, Pa_{O_2} and $\dot{Q}va/\dot{Q}t$ improved, even though peak airway pressures were not different from one another. Cardiac and stroke indices decreased somewhat (probably because of the higher mean AWP), but it should be noted that no attempt was made to avoid this reduction with either additional volume expansion or inotropic agents.

Discussion

The data presented here demonstrate that HFJV is effective in conjunction with commonly used levels of PEEP as a means of reversing the hypoxemia associated with severe lung injury induced acutely by oleic acid. These results are supportive of reported animal and clinical experiences (2, 3, 8). In comparison to CV, HFJV was not as effective at decreasing $\dot{Q}va/\dot{Q}t$ at the same PEEP or mean AWP, but was equally effective at the same peak AWP.

In these experiments, observations were made as paired comparisons, in which the order of ventilator sequence was random at each level of PEEP. Thus, the changes seen cannot be ascribed to the natural course of the lung insult.

Mechanical ventilation exerts its influence on cardiac output primarily through its effect on AWP. By design, PEEP was the same when HFJV was compared with CV in the first group of experiments. Mean

AWP was also comparable at each level of PEEP. Thus, no significant differences in cardiac or stroke indices were observed.

Some comparisons were made at different levels of "alveolar ventilation" (as determined by Pa_{CO_2}), as higher driving pressures (40 psi) resulted in greater CO_2 elimination in these cases. Our intention here was to maximize gas velocity to optimize our chances of observing "enhanced diffusion" to low $\dot{V}/\dot{Q}$ areas, as this mechanism has been invoked as a possible reason for reported improvements in oxygenation (4, 10). Consequently, Pa_{CO_2} tended to be lower during HFJV than during CV. As venous admixture actually increased under these circumstances, other combinations of driving pressure, rate, and inspiratory time were tried. The result was less hypocapnia, but the decrease in arterial oxygenation persisted. These differences in Pa_{CO_2} might have influenced arterial oxygenation in several ways, none of which change our conclusion that venous admixture increased with HFJV. First, although respiratory alkalosis can result in a decrease in Pa_{O_2} by depressing cardiac output (11), we observed no differences in cardiac output between CV and HFJV. Second, a lower Pa_{CO_2} can result in an increase in oxygen consumption. Although this would decrease mixed venous oxygen tension, the calculated venous admixture would not be affected by this change alone. Third, a lower Pa_{CO_2} can cause a shift to the left of the oxygen-hemoglobin dissociation curve. This, too, would cause a decrease in mixed venous P_{O_2} but would not by itself change mixed venous oxygen content, leaving the calculated venous admixture unaffected. Finally, even when comparisons were made at the same Pa_{CO_2} (8/24 total comparisons), the same directional changes in arterial P_{O_2} and $\dot{Q}va/\dot{Q}t$ were seen. Thus, although the lower levels of Pa_{CO_2} during HFJV at each level of PEEP might explain some of the differences seen in Pa_{O_2}, they do not account for the differences in venous admixture.

We have found, therefore, that although HFJV in combination with PEEP could reverse hypoxemia caused by oleic acid infusion to control levels, arterial oxygenation was routinely lower during HFJV than during CV at comparable levels of PEEP, mean AWP, and F_{IO_2}. The importance of taking AWP into account in such comparisons has been recently emphasized (12, 13).

Little evidence exists to support the notion that oxygenation might actually improve during high-frequency ventilation. Reports that make such claims (1, 2) are based on comparisons made at different airway pressures or F_{IO_2} (12). On the other hand, the available experimental data in animals are supportive of our findings. Thompson et al (14), for instance, found no improvement in Pa_{O_2} during high-frequency oscillation when comparisons were made at the same mean airway pressure. Gallagher and Banner (15), using a system similar to ours, reported that Pa_{O_2} was lower and shunt fraction higher during high-frequency ventilation at the same level of PEEP. These differences were not statistically significant, probably because the number of animals was small. Although our own data do not provide any direct evidence as to why oxygenation should be worse during HFJV, even at comparable airway pressures, it seems reasonable to speculate that ventilation was probably maldistributed with respect to perfusion during HFJV in this experimental model. Progressive atelectasis may be responsible for some of this maldistribution during HFV. Recent work (16, 17) suggests that such atelectasis may be reversible by periodic hyperinflation. Kolton et al (16) reported that oxygenation during HFV might actually be improved compared with CV if mean AWP is greater than the opening pressure of collapsed lung segments in the oleic acid-injured lung. However, at least 15 cm H_2O was required as opening pressure in their experiments, just slightly less than the mean airway pressures used by us in dogs treated with 10 torr of PEEP. Such pressures are usually in excess of what is necessary to improve oxygenation for clinical purposes without hemodynamic compromise. Furthermore, it is not clear how often such periodic hyperinflation would need to be repeated. In any event, although some investigations of gas exchange during high-frequency ventilation have emphasized possible mechanisms of improved gas transport down the airways (18, 19), our data and that of others (16) suggest that the distribution of ventilation within the lung is a matter of equal concern.

Although it is essential that comparisons of these ventilator modes be made at comparable levels of PEEP or mean AWP, and F_{IO_2}, in order to sort out the causes for observed changes in arterial oxygenation, the results of the experiments made at different levels of PEEP but at the same peak AWP, are still of clinical relevance. In these experiments, although peak AWP was maintained at the same level, $\dot{Q}va/\dot{Q}t$ decreased as PEEP was increased from 8 to 12 torr in changing from CV to HFJV. Cardiac output also decreased at the higher level of PEEP, probably because of higher mean AWP, but no attempt to counteract this effect with blood volume expansion or inotropic agents was made. These results are similar to those reported by Kolton et al (16) for high-frequency oscillation. Thus, when the use of higher levels of PEEP with CV is limited by high peak AWP, the use of HFJV (as in the experiments in the second group) may be clinically advantageous.

The smaller tidal volumes and thus potentially lower peak airway pressures associated with HFJV constitute potentially important clinical advantages. This has been shown dramatically by Carlon et al (2) in a series of patients with pulmonary airway disruption, a particularly difficult problem with commonly used methods of mechanical ventilation. Likewise, we have effectively used HFJV in a patient who developed respiratory failure shortly after pneumonectomy in which high peak airway pressures posed the threat of bronchial stump disruption (3).

Based on the present experiments, then, HFJV may be of value during acute hypoxemic respiratory failure in the following clinical circumstances: (a) when the primary goal is to reduce peak AWP (in such a case, the need for additional increases in either PEEP or F_{IO_2} should be anticipated); (b) when increases in PEEP, in order to reduce F_{IO_2} from nontoxic levels, are limited by peak AWP; (c) when CO_2 elimination is inadequate during CV, especially when this is the result of a bronchopleural fistula.

ACKNOWLEDGMENTS

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Reduction in Halothane Anesthetic Requirement by Clonidine, an Alpha-Adrenergic Agonist

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The effects of clonidine, a potent central alpha-adrenergic agonist, and of tolazoline, an alpha-adrenergic antagonist, on the minimal anesthetic concentration (MAC) of halothane were studied in male mongrel dogs. Control halothane MAC was 0.8 ± 0.04 vol% (determined in each dog by gas chromatography of arterial blood, n = 30). Clonidine, 5 μg/kg (n = 10) and 20 μg/kg (n = 10), given slowly intravenously, maximally reduced MAC by 42% (at 2.3 hours after clonidine) and 48% (at 2.6 hours after clonidine) for each dose. In another set of animals (n = 5) an alpha-adrenergic antagonist, tolazoline, 5 mg/kg IV, reversed the clonidine-induced reduction in halothane MAC rapidly and completely. Tolazoline alone, 5 mg/kg, (n = 5) had no significant effect on halothane MAC. Thus, the administration of the central alpha-adrenergic agonist clonidine decreased the required anesthetic concentration of halothane, as defined by MAC, by almost half. This effect, as it is reversed by tolazoline, is likely to be mediated through a central alpha-adrenergic receptor mechanism.

CLONIDINE is used clinically as an antihypertensive agent. Its action is attributed to a reduction in central sympathetic outflow mediated by stimulation of central alpha-adrenergic receptors (1-3). Clinical side effects of clonidine include sedation and dry mouth (4); additionally, this drug has produced and prolonged sleep experimentally in man (5, 6) and animals (7, 8). Clonidine is a potent central analgesic in animal models (9). It has been shown to be 60 and 10 times more potent on a weight basis than morphine in producing analgesia in mice (10, 11); however, clonidine-induced analgesia is not reversed by naloxone. In contrast, naloxone has been claimed to reverse the antihypertensive effects of clonidine (12). Tolerance to both the sedative (13) and the analgesic (14) effects of clonidine develops rapidly.

Because clonidine is an analgesic and, when administered acutely, results in profound sedation, it was felt that acutely administered clonidine would have the potential to modify anesthetic requirement. The

experiments that were conducted to test this hypothesis had three purposes: (a) to determine whether clonidine administered acutely intravenously would affect the potency of halothane; (b) to determine the ability of tolazoline, an alpha-adrenergic antagonist, to affect or reverse any clonidine-induced changes in the anesthetic requirement of halothane; and (c) to determine the effect of tolazoline alone on halothane requirement.

Methods

Anesthesia was induced in unpremedicated male mongrel dogs with halothane by mask; care was taken to avoid unnecessary noise and motion. Cuffed tracheal tubes were inserted under deep halothane anesthesia and anesthesia was then maintained with 1.5% inspired halothane in oxygen during preparative surgery and instrumentation. Blood pressure was measured from a femoral arterial cannula by a Hewlett-Packard transducer (model 1280) and recorded on a direct-writing polygraph (Hewlett-Packard no. 7758). End tidal CO_2 was measured and recorded by a Beckman LB-3; ventilation was adjusted to maintain Pa_{CO_2} at 35 ± 2 torr. Arterial blood gas tensions were periodically measured using a Corning 165 blood gas analyzer. Core temperature was monitored with an

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esophageal temperature probe and maintained at 39 ± 1°C. Halothane levels in arterial blood were determined by gas chromotography according to the equilibration method of Fink and Morikawa (15).

Determination of MAC

Once each animal had stabilized for at least 1 hour, the inspired halothane was reduced to 1.2% for 30 minutes before starting the experimental protocol. Minimum anesthetic concentration (MAC) of halothane was used as the measure of anesthetic potency and was determined by the now standard methods of Eger et al (16), except that arterial blood halothane concentration was used in lieu of end-tidal halothane concentration. Each animal was equilibrated at a test concentration of halothane for 20 minutes. A tail clamp was applied (Carter resection clamp) for 1 minute. This procedure was repeated after stepwise reduction of the inspired concentration of halothane by 0.1% until a purposeful movement was elicited. Then the concentration of the inspired halothane was increased by 0.1% until no movement was noted. The MAC of halothane was calculated as the mean of these two halothane arterial blood levels. This procedure was repeated to confirm the stability of control MAC.

Three types of experiments were carried out. (a) Clonidine, 5 or 20 μg/kg, was given slowly by intravenous drip (approximately 1 μg/kg/min). MAC was measured repeatedly until 5 hours after the 5-μg/kg dose and 8 hours after the 20-μg/kg dose of clonidine (10 dogs per dose). "Time after clonidine" was considered to begin at the time administration of clonidine was started. (b) The effect of the alpha-adrenergic antagonist tolazoline on MAC after clonidine was determined in another set of five dogs. In this series, each dog was treated as described above for the group given 20 μg/kg of clonidine; that is, MAC was measured and confirmed before and for 2.3 hours after the intravenous injection of 20 μg/kg of clonidine. Before tolazoline administration, the inspired halothane was, in most dogs, increased to a value 0.2% higher than control MAC for each animal and stabilized for 25 minutes. Then tolazoline, 5 mg/kg, was given intravenously, and MAC was again determined during the following hour. (c) To determine whether an intravenous injection of tolazoline alone (5 mg/kg) affects halothane MAC, a separate set of five dogs was used. In each, control MAC was determined as previously described. Tolazoline was then given and MAC redetermined and confirmed over the next hour.
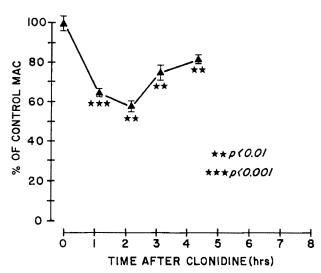
FIG 1. Changes in halothane MAC with time following intravenous clonidine, 5 μg/kg, in dogs. Control, time zero, represents pooled mean ± SEM, n = 30. Each remaining point is shown as mean ± SEM, (n = 10).

Analysis of variance was used to test all individual groups of data. Comparisons involving data obtained before and after drug administration were made by paired t-tests with $p < 0.05$ regarded as being statistically significant. Percent change was reported as the difference between the control and the experimental condition for each animal. All values are reported as means ± SEM. Drugs used were clonidine (Boehringer Ingelheim) and tolazoline (Sigma Chemical Co.).

Results

No statistically significant difference was found (one-way analysis of variance, $p < 0.05$) between the MAC values for any of the control groups used, and therefore all groups were combined to give a mean control value for halothane MAC of 0.8% ± 0.04% (n = 30).

Clonidine, 5 μg/kg IV

Injections of 5 μg/kg of clonidine (n = 10) decreased MAC of halothane by 36% after 1.2 hours. Maximal decrease (42%) occurred after 2.3 hours and by 3.1 hours the effect had reverted toward control values with only a 25% reduction in MAC. After 4.4 hours, MAC still showed a 19% decrease when compared with control values (Fig 1).

Clonidine, 20 μg/kg IV

As seen in Fig 2, 20 μg/kg of clonidine (n = 10) also reduced MAC. This dose of clonidine caused a

maximal 48% reduction of halothane MAC after 2.6 hours. By 3.3 hours, the effect of clonidine had waned to a 40% decrease when compared with control values. By 7.3 hours after clonidine administration, MAC had returned to within 5% of control values.

Neither the 5-μg/kg nor the 20-μg/kg dose of clonidine resulted in a significant reduction in systemic blood pressure during halothane anesthesia. Clonidine, given at a faster rate, increased blood pressure secondary to peripheral alpha-adrenergic stimulation. Heart rate was decreased significantly from 100 ± 4 to 83 ± 6 beats per minute at the control halothane MAC level.

Tolazoline, 5 mg/kg IV

Tolazoline did not significantly (n = 5, p > 0.05) alter halothane anesthetic requirement, as determined by MAC, during the 1-hour observation period.

Clonidine-Tolazoline

In the third protocol, when clonidine, 20 μg/kg IV, was given as before, MAC decreased 43% ± 3% (n = 5) below control levels after 2.3 hours. Approximately 2.5 hours after clonidine administration, during the clonidine-induced reduction of MAC, 5 mg/kg of tolazoline was given. After tolazoline administration, halothane MAC was not significantly different from control levels (105% ± 6%). Thus, tolazoline reversed the clonidine-induced decrease in halothane anesthetic requirement as determined by MAC (Fig 3). In three early experiments in which the halothane had
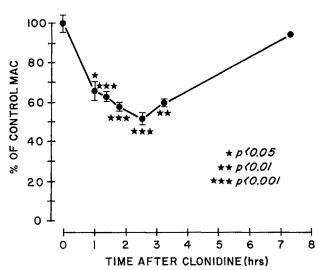
FIG 3. Reversal of clonidine-induced (20 μg/kg) reduction in halothane MAC by tolazoline, 5 mg/kg (given as indicated by arrow [O]). For comparison, the curve showing the effect of 20 μg/kg of clonidine (Fig 2) is repeated (●).
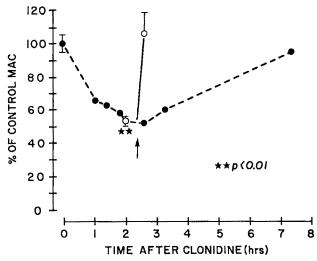
been kept at the MAC level associated with clonidine, tolazoline caused immediate awakening even before the injection had been completed. In subsequent experiments the inhaled concentration of halothane was increased to approximately 1.2 times the control MAC before the tolazoline was injected to prevent awakening (see "Methods").

Discussion

The results show that acutely administered clonidine (20 μg/kg) reduced halothane anesthetic requirement in dogs by a maximum of 48%. Work by other investigators has shown that other drugs affecting the central adrenergic system can also alter anesthetic requirements. Two drugs that alter halothane MAC in opposite directions, for example, and that also have opposing effects on the central adrenergic system, are reserpine and acutely administered amphetamine. Reserpine depletes central and peripheral catecholamine (17) (and serotonin) stores and, at doses that substantially reduce catecholamine levels, reserpine decreases halothane MAC by 33% (18). Conversely, acutely administered amphetamine, which facilitates adrenergic action through transmitter release and direct stimulation of adrenergic receptors, increases MAC in a dose-dependent fashion (19). However guanethidine, a peripheral catecholamine depleter with no central effects, does not affect MAC (18). Together, these results suggest that an increase in central catecholaminergic activity leads to an increase in anesthetic requirement, whereas a decrease in central catecholamine activity reduces anesthetic requirement. Drugs

FIG 2. Changes in halothane MAC with time following clonidine, 20 μg/kg IV, in dogs. Control, time zero, represents pooled mean ± SEM, n = 30. Experimental points less than 4 hours are means ± SEM, n = 10, whereas 7.3-hour point (mean = 95 ± 10) (n = 3).

affecting only the peripheral adrenergic system have no effect on MAC.

Clonidine is a potent agonist of both the classical alpha-adrenergic receptor (alpha$_1$) and the more recently delineated alpha$_2$ receptor. This second type of alpha receptor, the alpha$_2$, has been shown to be reasonably distinct from the classic alpha receptor in several ways. A presynaptic location has been suggested for the alpha$_2$ receptor, activation of which inhibits norepinephrine release and decreases norepinephrine turnover (20). Clonidine, acting on a presynaptic alpha$_2$ receptor, would be expected to inhibit norepinephrine transmitter release, and thus decrease neuronal adrenergic function. Clonidine resulted in a reduction in the halothane anesthetic requirement rather than increasing it as might be expected by an adrenergic agonist. However, the ability of the drug to decrease catecholamine output by stimulation of the presynaptic alpha$_2$ receptor offers an explanation for this apparent paradox and renders our observations consistent with the conclusions of previous workers (i.e., a decrease in anesthetic requirement with a reduction in synaptically available catecholamine). It is of interest that Drew et al (21) have shown that clonidine-induced sedation in the rat is mediated by what they considered to be a presynaptic alpha$_2$ receptor.

It should be noted that some authors (22, 23) who have studied the hypotensive actions of clonidine have postulated the existence of a central inhibitory postsynaptic clonidine (alpha$_2$) receptor. A postsynaptic site of action of clonidine would require a more complex mechanism. Clearly, more work needs to be done to clarify fully the exact site(s) and mechanism(s) of action of clonidine. Alpha-methyldopa has also been shown to decrease MAC (18) and although this drug might be similar to clonidine, its mechanism of action is not clearly understood.

The only previous report (24) concerning the effect of clonidine on MAC deals with chronic administration (50 μg/kg three times a day). Under these circumstances, clonidine was found to potentiate halothane anesthesia by only 14.5% (24). This observation of only a small increase in halothane potency during chronic administration of clonidine is compatible with the rapid development of tolerance observed with both the sedative (13) and the analgesic (14) effects of clonidine.

Clonidine is a more potent analgesic than morphine when compared on a weight basis in various animal models. Recently, evidence for a link between the analgesic activity of clonidine and the endogenous opiate system has been reported. In rats, 500 μg/kg of clonidine more than doubled the plasma beta-endorphin levels within 15 minutes (25). It remains to be determined not only whether lower doses of clonidine, such as those used in the present study, can also be linked to the endogenous opiate system, but also whether clonidine-induced analgesia plays a role in the clonidine-induced reduction in halothane anesthesia requirement. However, since naloxone has been shown not to reverse clonidine analgesia (11), such a role appears unlikely.

In this study, tolazoline reversed the effect of clonidine so that MAC was returned to a value not significantly different from control levels, yet tolazoline did not significantly affect halothane MAC by itself. These findings lead to two possible conclusions. First, no significant proportion of halothane anesthesia as measured by MAC involves an adrenergic function that can be blocked by tolazoline. Second, the effect of clonidine on halothane requirement is a function of alpha-adrenergic stimulation (either alpha$_1$ or alpha$_2$, as tolazoline antagonizes both).

Many central nervous system depressant drugs are known to reduce the required effective concentration of inhalation anesthetic agents. Narcotics, barbiturates, and benzodiazepines are in daily clinical use for this purpose. However, all of these drugs are respiratory depressants in the doses used. Clonidine has not been reported to have respiratory depressant effects, and in our preliminary observations (unpublished data) the effective doses of clonidine did not depress spontaneous ventilation. This question requires further study, but the possibility exists that clonidine increases the therapeutic ratio of halothane by decreasing the anesthetic requirement without potentiating the respiratory depressant effect.

Thus, we have shown that clonidine (5 and 20 μg/kg) causes a marked decrease in halothane anesthetic requirement in the dog. This effect is mediated through an alpha-adrenergic mechanism underscoring the significance of the central adrenergic system. Other investigators have previously shown that clonidine is a potent analgesic, a sedative and that it decreases central sympathetic outflow. No other nonopiate class of drugs offers so many actions important to anesthesia. Clonidine and clonidine-related compounds deserve future consideration in anesthesia research as potential modifiers of anesthetic actions.

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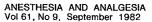
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Neural Blockade and Pharmacokinetics following Subarachnoid Lidocaine in the Rhesus Monkey I. Effects of Epinephrine

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A sensitive and reliable animal model for the objective physiologic and pharmacokinetic evaluation of spinal anesthesia has been developed. Using this model, spinal anesthesia using lidocaine (30 mg) in 7.5% dextrose with and without epinephrine was compared. Epinephrine did not alter the degree or duration of time to achieve maximum motor block. However, epinephrine did significantly increase the time for complete motor recovery. A significantly higher dermatome level of sensory block was achieved in the epinephrine-containing solutions, as well as a significantly longer time for complete recovery. This reflects a latent effect of epinephrine, as the time for two-segment regression was independent of epinephrine. Pharmacokinetic analysis showed no effect of epinephrine on absorption and elimination constants. The maximum plasma concentration and time to reach maximum plasma concentration were equal with and without epinephrine.

THE EFFICACY of adding epinephrine to local anesthetic solutions for spinal anesthesia is still in question (1–3). This is due in part to the wide diversity of results from various reported studies. For example, tetracaine solutions that contain 0.2 mg of epinephrine have been reported to prolong spinal anesthesia by 12% to 53% (2). Similar diversity has been reported for lidocaine solutions containing epi-

nephrine, ranging from 0% to 60% prolongation (3). These studies, however, looked only at the time from injection of local anesthetic to complete return of sensory cutaneous feeling. Although a few studies have been done using other doses of epinephrine, clinical responses did not seem to be dose related, with the resulting 0.2-mg dose becoming common clinical practice.

A more recent study (4), comparing plain and epinephrine-containing solutions of 5% lidocaine for spinal anesthesia, divided the periods of sensory and motor anesthesia as follows: (a) the time period required to sustain total motor and sensory anesthesia, and (b) the time to recover complete neural function. Their results showed no effect of epinephrine in prolonging the period of total anesthesia, but a significant delaying effect on the recovery phase of both motor and sensory function.

Three mechanisms for prolongation of neural blockade by epinephrine have been proposed: (a) reduced drug absorption secondary to vasoconstriction, (b) inhibition of the enzymes responsible for the metabolism of local anesthetics, and (c) direct action on neural elements (2).

We have recently established a rhesus monkey

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model for spinal anesthesia which is a reliable and sensitive method for evaluation of both physiologic responses and the pharmacokinetics of uptake and elimination (5, 6).

This study was undertaken to assess not only the effect of epinephrine on the neural blocking properties of 5% lidocaine in the subarachnoid space of the primate model, but also to assess any alterations that epinephrine might induce in the pharmacokinetics of the subarachnoidally administered lidocaine.

Methods

Six adult rhesus monkeys were used in a three-way crossover design. Each animal received the three treatments described below in random order with a 5-week rest period between treatments. The three study treatments were: (a) 30 mg of lidocaine intravenously, (b) 30 mg of 5% lidocaine in 7.5% dextrose intrathecally, (c) 30 mg of 5% lidocaine in 7.5% dextrose containing epinephrine intrathecally.

The primate colony is under the care of a full-time veterinary staff. The animals are housed individually in squeeze cages approved by the American Association for Accreditation of Laboratory Animal Care (AAALAC) and were fed a diet of Purina monkey

chow once a day with water ad libitum from an automatic watering system. Monkeys were tested for tuberculosis by intradermal eyelid injection of purified protein derivative (PPD) monthly and by chest roentgenogram each 90 days. All animals were housed in rooms on a 12-hour light-dark cycle with controlled temperature and humidity.

Experimental Procedure

Fasting animals were sedated with ketamine (10 mg/kg IM) and transported to the laboratory. Under light general anesthesia (0.5% halothane, N_2O/O_2 [3L/2L]) cannulas were placed as follows: (a) in peripheral vein for injection of lidocaine (group 1) and maintenance fluids of 5% dextrose and lactated Ringer's solution via an infusion pump, and (b) in a saphenous artery for blood and gas sampling.

Arterial blood samples (4 ml) were drawn at 0, 4, 7, 10, 15, 20, 25, 30, 45, 60, and 90 minutes, and hourly thereafter for a total of 5 hours. Blood volume was restored using normal saline on a 3:1 basis. Samples were allowed to clot, with centrifuged serum analyzed by gas chromatography for lidocaine concentrations (7).

Intravenous and Subarachnoid Injections

Subsequent to cannulation, the three groups were managed as follows:

Group 1. Animals in this group were placed in the sitting position in a primate restraining chair and given 30 mg of 2% lidocaine intravenously during a 1-minute injection period.

Groups 2 and 3. Animals in these groups were placed in the right lateral decubitus position for placement of a 22-gauge (4-cm) needle into the subarachnoid space. A midline approach at the L5–6 interspace was used. After free flow of cerebrospinal fluid was obtained, two animals received 0.6 ml of commercially prepared 5% lidocaine (30 mg) and 7.5% dextrose. In group 3, animals received the same solution containing epinephrine (the epinephrine solution was prepared by adding 0.2 ml of 1:1000 epinephrine to the ampule of commercially prepared lidocaine before the aspiration into the syringe of the 30-mg dose). After injection of the study drug, the spinal needle was flushed with 0.1 ml of air and withdrawn. Animals remained in the level supine position for 90 seconds and were then placed in the sitting position in the primate chair for the duration of the experiment. The measurements of neural blocks were identical with those previously reported (5).

	DEFINITIONS
A	for intravascular injection, A is the intercept of the distribution slope α with the ordinate; for subarachnoid injection, A is the intercept of the monoexponential absorption slope with the ordinate
α	distribution rate constant
AUC (0–∞)	area under blood concentration-time curve from zero to infinity
B	intercept of monoexponential elimination slope with ordinate
β	elimination or slow disposition rate constant
Cl < tot >	total plasma clearance
C (max)	maximum plasma concentration following subarachnoid injection
F	fraction of drug absorbed following subarachnoid injection
k_a	rate of drug absorption following subarachnoid injection
kel	elimination rate constant
t (lag)	lag time for systemic absorption following subarachnoid injection
t (max)	time which corresponds to C (max) following subarachnoid injection
Vdβ	volume of distribution during elimination or slow disposition phase

Pharmacokinetic Analysis

Intravenous blood concentration-time data were analyzed in two ways: (a) data were fit to an intravascular open two-compartment model using standard computer programs, and (b) parameters were calculated independent of compartment model using the area under the blood-concentration time curve [AUC(0-∞)]. AUC(0-∞) was estimated using the linear trapezoidal rule (8). All pharmacokinetic symbols are defined below.

Blood concentration data in groups 2 and 3 were analyzed in the following manner: (a) Data were fit to an open one-compartment model for extravascular injection. (b) Parameters were calculated independent of compartment model using the area under the plasma-concentration time curve [AUC(0-∞)]. (c) The fraction of drug absorbed (F) following a subarachnoid treatment was calculated using the following equation (BW, body weight; IV, intravenous; XV, subarachnoid) (8):

$$F = \frac{AUC(0-\infty)_{XV} \times \dfrac{dose\ (IV)}{BW(IV) \times \beta(IV)}}{AUC(0-\infty)_{IV} \times \dfrac{dose\ (XV)}{BW(XV) \times \beta(XV)}}$$

Each blood-concentration time curve following subarachnoid injection was examined for evidence of a lag time in systemic appearance of lidocaine using the following equation (8):

$$t(lag) = \frac{\ln A/B}{ka - kel}$$

Statistical Treatment of Data

All data are presented as means ± SEM. Statistical analyses were accomplished using either the *t*-test for paired data, Student's *t*-test, or Schefe's test for variance for intragroup and intergroup comparisons when appropriate; $p < 0.05$ was considered the minimal level of statistical significance. Solutions of the blood concentration-time curves were tested for "goodness of fit" by calculation of standard coefficients of determination (R^2). $R^2 > 0.9$ for 12 to 15 points were considered appropriate solutions for the biexponential blood level equation. Additionally, values for AUC(0-∞) estimated from parameters derived by compartment model solutions were compared with the actual AUC(0-∞) obtained by integration of the blood-concentration time data. If the differences between the estimated and actual AUC(0-∞) were not significant, the selected model was considered appropriate.

Results

Neural Blockade (Groups 2 and 3)

The initial onset of sensory and motor anesthesia was equally rapid in both groups (approximately 2 to 4 minutes). Also equal between groups 2 and 3 was the duration of maximum motor and sensory anesthesia. Differences occurred in group 3 (epinephrine group) in the measurement of a significantly higher level of sensory blockade and a simultaneous, but significantly prolonged, period of complete recovery of both sensory and motor elements. Although the duration of maximum motor blockade tended to be longer than the duration of maximum sensory anesthesia (as judged by two-segment regression) in both groups, this difference was not statistically significant (Tables 1 and 2).

Pharmacokinetics

A comparison of the pharmacokinetic parameters obtained for intravenous lidocaine using open two-compartment model and model-independent calculations resulted in a close correlation. The close correlation between the two methods demonstrates that fitting data to an open two-compartment model is

TABLE 1

Motor Blockade following Subarachnoid Lidocaine (30 mg) with and without Epinephrine*

Epinephrine	Motor block score	Duration of complete motor block	Time to complete motor recovery
		min	
+	6.0 ± 0	61 ± 14	178 ± 19†
−	5.6 ± 0.3	58 ± 8	108 ± 6

* Values are means ± SEM (N = 6).

† $p < 0.01$ when compared with lidocaine without epinephrine.

TABLE 2

Sensory Blockade following Subarachnoid Lidocaine (30 mg) with and without Epinephrine*

Epinephrine	Level (dermatome)	Time for 2-segment regression	Time for complete sensory recovery
		min	
+	T-8 ± 1†	36 ± 7	179 ± 13‡
−	T-11 ± 1	37 ± 7	98 ± 13

* Values are means ± SEM (N = 6).

† $p < 0.05$ when compared with lidocaine without epinephrine.

‡ $p < 0.01$ when compared with lidocaine without epinephrine.

appropriate. For the open two-compartment model, the AUC(0–∞) is estimated by $A/\alpha + B/\beta$ (Table 3) (8).

A comparison of pharmacokinetic parameters obtained for the three lidocaine treatments using the model-independent method clearly illustrates that time to peak concentration [t(max)], peak concentration [C(max)], and AUC(0–∞) are independent of epinephrine (Table 4). Lidocaine was completely absorbed in both subarachnoid treatments, as demonstrated by the fraction of drug absorbed. The elimination phase volumes of distribution were found to be statistically greater for the epinephrine group. However, no differences were found when these values were normalized to body weight. Total clearances were found to be independent of the route of lidocaine administration (Table 4).

A comparison of the pharmacokinetic parameters obtained in groups 2 and 3 was made by fitting the blood concentration-time data to an open one-compartment model. The AUC(0–∞) for a one-compartment model for intravascular injection is estimated by (8):

$$AUC(0-\infty) = \frac{B}{kel} - \frac{A}{ka}$$

The extremely close correlation between the values obtained from the open one-compartment model and the AUC(0–∞) obtained from integration of the blood-concentration time curve (Table 4) demonstrates that the open one-compartment model is appropriate for the estimation of absorption constants. The rates of absorption following subarachnoid lidocaine are independent of added epinephrine in the rhesus monkey (Table 5). The only significant differences between treatment groups were the apparently higher central compartment volumes in animals given epinephrine. However, normalizing these volumes to body weight removed any differences. Calculations based on solutions obtained from open one-compart-

TABLE 3

Parameters Obtained from Open Two-Compartment Model and Compartment-Model Independent Solutions for Blood Concentration Time Data following Intravenous Lidocaine*

Parameter	Two-compartment	Independent
β (L/hr)	0.49 ± 0.11	0.44 ± 0.09
AUC(0–∞) [(μg/ml)] hr]	2.5 ± 0.2	2.6 ± 0.3
Cl<tot> (L/hr)	12.0 ± 1.1	11.8 ± 0.7
Vdβ (L)	31.8 ± 5.9	34.1 ± 6.6
Vdβ (L/kg)	4.5 ± 0.8	4.8 ± 0.8

* Values are means ± SEM (N = 6).

TABLE 4

Pharmacokinetic Parameters Obtained Independent of Compartment Model for Intravenous Lidocaine and Subarachnoid Lidocaine with and without Epinephrine*

Parameter	With epinephrine	Without epinephrine	Intravenous
t(max) (hr)	0.47 ± 0.09	0.51 ± 0.09	—
C(max) (μg/ml)	1.1 ± 0.1	1.3 ± 0.2	—
AUC(0–∞) [(μg/ml) hr]	2.1 ± 0.4	2.6 ± 0.4	2.6 ± 0.3
F	1.02 ± 0.20	0.98 ± 0.16	—
β (1/hr)	0.42 ± 0.05	0.46 ± 0.05	0.44 ± 0.09
Vdβ (L)	38.8 ± 7.7†	25.7 ± 4.0	34.1 ± 6.6
Vdβ (L/kg)	4.1 ± 0.6	3.7 ± 0.5	4.8 ± 0.8
Cl<tot> (L/hr)	12.4 ± 1.7	10.9 ± 1.1	11.8 ± 0.7

* Values are means ± SEM (N = 6).

† $p < 0.05$ when compared with lidocaine without epinephrine.

TABLE 5

Pharmacokinetic Parameters Obtained for One-Compartment Model for Subarachnoid Injection of 5% Lidocaine with and without Epinephrine*

Parameter	With epinephrine	Without epinephrine
AUC(0–∞) [(μg/ml) hr]	2.1 ± 0.4	2.5 ± 0.4
k$_a$ (1/hr)	3.9 ± 0.2	4.2 ± 0.7
kel (1/hr)	0.53 ± 0.08	0.50 ± 0.01
Vc(L)	29.9 ± 3.8†	18.9 ± 3.3
Vc(L/kg)	3.0 ± 0.6	2.9 ± 0.6
Cl<tot> (L/hr)	15.5 ± 3.0	10.0 ± 1.3

* Values are means ± SEM (N = 6).

† $p < 0.05$ when compared with lidocaine without epinephrine.

ment analysis showed that neither group 2 nor group 3 exhibited a significant lag time for systemic absorption.

Discussion

In this study the addition of epinephrine to hyperbaric lidocaine spinal solutions resulted in statistically higher levels of sensory block than when plain lidocaine was used. This is in contrast to the report by Chambers et al (4), in which no significant differences were found in the highest dermatome blocked. This effect, which we noted, is not thought to be due to a change in volume (0.6 to 0.66 ml), as concurrent studies comparing 0.6 ml of 5% lidocaine in 7.5% dextrose (30 mg) with 1.5 ml of 2% lidocaine in 7.5% dextrose (30 mg) resulted in identical levels of sensory block. Our findings that the duration of complete sensory and motor anesthesia was independent of epinephrine are in agreement with the results in man reported by Chambers et al (4). Our findings of

prolonged recovery times for both motor and sensory function are also in agreement with those of Chambers et al (4).

Lidocaine was chosen for this study because a large amount of physiologic and pharmacokinetic data have been collected using the rhesus monkey (5, 6). The rhesus monkey model is capable of uncovering subtle pharmacokinetic changes as a function of composition of the local anesthetic solution (9). No differences in rates of absorption were detected between the two lidocaine solutions injected into the subarachnoid space. One explanation for this could be that initial vasoconstriction by epinephrine is extremely transient and is followed by normal absorption. This possibility was ruled out by calculating lag times for systemic absorption. No lag times were detected with or without epinephrine. Thus, the data presented here argue against that proposed mechanism of epinephrine prolongation of spinal anesthesia. In addition, identical values of t(max) and C(max) of lidocaine were found when lidocaine was injected either with or without epinephrine. This is in partial agreement with Axelsson and Widman (10), who reported that t(max) of lidocaine injected into the subarachnoid space was independent of added epinephrine, but C(max) was significantly higher following injection of lidocaine without epinephrine.

Lidocaine is extensively metabolized by liver enzymes and is a drug whose clearance is dependent on liver blood flow. As no changes in total clearance or elimination rates were detected for either treatment, the proposal that epinephrine acts by inhibiting the enzymes responsible for local anesthetic metabolism seems unlikely.

Our pharmacokinetic findings with lidocaine are similar to those reported by Converse et al (11) with tetracaine. They also found that epinephrine caused no differences in the rate of disappearance of tetracaine from cerebrospinal fluid (11).

The remaining explanation for prolongation of spinal anesthesia by epinephrine is that of a direct neural action. Pilot studies recently reported by Collins et al (12) suggest this may be the case. Although our study cannot support the validity of this mechanism, we can cast considerable objective doubt on the reality of either vasoconstriction or enzyme inhibition being the operative mechanism.

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Fentanyl Reduces the Intensity of Painful Tooth Pulp Sensations: Controlling for Detection of Active Drugs

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This study assessed whether experimentally determined narcotic analgesia in human subjects represents a pharmacologic effect or a psychological effect of detecting the administration of an active medication. Forty dental patients used a verbal descriptor procedure to assess both the intensity and unpleasantness of sensations produced by electrical stimulation of intact teeth. Stimuli were rated before and after an intravenous injection of 0.11 mg/kg of diazepam, to produce detectable side effects in all patients, followed by a double-blind intravenous injection of either 0.66 μg/kg of fentanyl or saline placebo. The results were similar to previous findings in which diazepam was not administered: only intensity responses were reduced after fentanyl administration and only unpleasantness responses were reduced after placebo administration. These results suggest that the reduction in pain intensity following fentanyl administration represents an analgesic effect and not an artifact of detecting the administration of an active medication. They also suggest that diazepam at this dose does not alter pain sensations produced by electrical tooth pulp stimulation.

A LARGE BODY of clinical evidence suggests that narcotics such as morphine and fentanyl produce analgesia by reducing primarily the unpleasantness rather than the intensity of pain sensations (1–4). However, a recent study (5) showed that the narcotic fentanyl reduced intensity judgments of painful sensations evoked experimentally by electrical stimulation of the tooth pulp. This result suggests that, in addition to affecting the unpleasantness of clinical pain sensations, narcotics produce analgesia by directly attenuating the intensity of pain sensations.

The fentanyl study (5), however, was susceptible to a source of bias present in almost all studies comparing active pharmacologic agents to inert placebos in human subjects. This bias results from the fact that patients taking active medications experience side effects to a degree greater than do those who receive

placebo. If a subject expects to receive either an active or inactive drug, side effects may provide sufficient cues that the active drug has been administered. These cues and the desire to perform well may result in an appropriate change in response behavior. Intravenous fentanyl produces immediate sensations of lightheadedness, dizziness, and nausea rarely found after the administration of saline placebo, and fentanyl's side effects may cue the subjects to lower their responses to the stimuli. An ideal active placebo would produce salient side effects without producing the test drug's pharmacologic action.

We have replicated the fentanyl study with the addition of a preinjection of diazepam in both the fentanyl and saline placebo groups. Diazepam was chosen because of its demonstrated emotional effect and evidence that it has little, if any, effect on pain sensation (6–15). Intravenous diazepam administration produces immediate subjective effects such as lightheadedness and dizziness. Administration of this drug to both those receiving fentanyl and those receiving placebo controls for the side effect artifact because all subjects experience the effects of an active drug. Diazepam also serves to mask the effects of a subsequent fentanyl injection, making it difficult for the experimenter to determine whether fentanyl had

been administered. With this improvement in both sides of the "double-blind," the following experiment assesses whether the analgesic effects observed for fentanyl in comparison to placebo are still found if drug administration is preceded by an injection of diazepam.

Methods and Materials

Eighteen men and 22 women, aged 18 to 45 years (median, 23 years) served as subjects. All were referred to the National Institute of Dental Research for extraction of third molar teeth. The purpose of the experiment was described, and informed consent was obtained in a preliminary first session approximately 1 week before each patient's oral surgery. The subjects were informed that they could withdraw from the experiment at any time. The research protocol was approved by a formally constituted National Institutes of Health Clinical Research Subpanel.

The experimental stimuli were assessed by the same verbal psychophysical procedures used in the fentanyl study (5). Each subject quantified the magnitude of verbal descriptors of sensory intensity or unpleasantness by ratio-scaling techniques, resulting in a numerical value for each descriptor. The same descriptors were used to rate experimentally produced pain sensations and these verbal responses were analyzed quantitatively by substituting each individual's numerical value for each verbal response.

The verbal descriptors used for pain responses were quantified in two steps. In the first step, subjects were instructed to use a handgrip dynamometer or a time-duration button to make responses proportional to the lengths of seven lines ranging from 1.3 to 33 cm in equal log steps presented twice randomly. These stimuli were rear projected on a 37x38-cm translucent screen. The handgrip measure was performed by squeezing a commercial 0 to 50 kg hand dynamometer in proportion to stimulus magnitude. A potentiometer produced an output voltage recorded by a digital sample-and-hold circuit with a resolution of 0.05 kg. Proportional time-duration responses were made by pressing a button that activated a millisecond timer and an auditory cue.

Mean log handgrip and time-duration responses were determined individually for each line stimulus. Linear regressions of mean log response against mean log line length resulted in linear functions for each response measure. The slopes of these functions, power function exponents in arithmetic units, calibrated each individual's use of a specific response with a known, measured stimulus. In the second step,

subjects used the handgrip and time-duration response to rate the magnitude of intensity or unpleasantness implied by 12 descriptors of sensory intensity (i.e., mild, moderate, intense) and 12 descriptors of unpleasantness (i.e., annoying, unpleasant, distressing) presented twice randomly. The calibration exponents determined in the first step were used to transform mean responses to each descriptor from units of handgrip force or time duration to common units of line length, referred to as units of relative magnitude. This procedure, described in detail elsewhere (16–18), reduces scaling biases and standardizes responses within and between individuals so that different responses can be compared and combined within individuals, and compared between individuals. Average responses for each individual produce a unique scale of the sensory intensity or unpleasantness implied by each word that is used subsequently to quantify individual verbal responses to the tooth pulp stimuli.

Following verbal scaling, the pain range for the tooth pulp stimulator was determined. A saliva injector was placed in the mouth and a central incisor was isolated with cotton rolls and carefully dried. The stimulating probe, consisting of a notched polyethylene cylinder attached to a metal handle, was placed on the incisal edge of the isolated tooth and held in place by the subject. Electrical contact was maintained by a silver electrode and conductive paste. The metal handle served as a ground electrode. Immediately preceding each stimulus, a 5-second air stream was forced through a hole in the cylinder and directed against the anterior surface of the tooth to both signal the stimulus and dry the tooth. Tooth impedance was monitored on each trial to ensure tooth dryness and isolation of the stimulus from surrounding soft tissue structures. The tooth stimuli consisted of 1-second trains of monopolar, monophasic, cathodal, 1-msec constant current pulses delivered to intact, upper central incisors at 100 Hz. These parameters were chosen to stimulate pulpal fibers exclusively without either activation of fibers in adjacent periodontal and gingival tissue or significant polarization of the electrode or tooth (19, 20). Sensory threshold, pain threshold, and pain tolerance were determined by a modified method of limits. The intensity of successive stimuli delivered at 10-second intervals was increased in 1-μamp steps. The subject used finger signals to indicate the intensity first detected, the point at which the sensation became painful, and the maximally tolerated intensity. This procedure was repeated, and values for pain threshold and tolerance were used to

compute the intensities of seven discrete stimuli varying in equal log steps between these values.

The second session began 1 hour before the scheduled oral surgery procedure. The subject was prepared for tooth pulp stimulation and the seven stimuli were presented at 20-second intervals, six times each in random order. These 42 stimuli were scaled by pointing to appropriate descriptors printed on a card in random order. Twenty randomly chosen subjects used descriptors of sensory intensity and the remaining 20 subjects used descriptors of unpleasantness. After initial scaling, either a combination of 0.11 mg/kg of intravenous diazepam and saline or a combination of 0.11 mg/kg of diazepam and 0.66 μg/kg of fentanyl was administered in a double-blind fashion. After a 5-minute pause, another set of 42 stimuli was presented and scaled.

Results

The relative magnitudes determined for each descriptor by each subject are shown in Table 1. Mean log sensory intensity responses plotted against the seven tooth pump stimuli are shown in Fig 1. The four functions show mean responses before and after the administration of diazepam with fentanyl (Fig 1, A) and before and after the administration of diazepam with saline (Fig 1, B). Effects of the intravenous

TABLE

Ratio-Scaled Relative Magnitudes Determined for Sensory Intensity and Unpleasantness Descriptors*

Sensory intensity		Unpleasantness	
Descriptor	Relative magnitude	Descriptor	Relative magnitude
Extremely intense	72.1	Very intolerable	37.4
Very intense	48.7	Intolerable	25.4
Intense	33.4	Very distressing	19.6
Slightly intense	21.3	Slightly intolerable	13.3
Strong	21.2	Very unpleasant	11.5
Barely strong	12.8	Distressing	11.5
Moderate	12.5	Very annoying	11.4
Mild	4.6	Slightly distressing	6.7
Very mild	2.9	Annoying	6.4
Weak	2.7	Slightly annoying	4.4
Very weak	2.0	Unpleasant	4.4
Faint	1.7	Slightly unpleasant	3.3

* Each magnitude was determined by cross-modality matching perceived handgrip force or duration of button press to magnitude of sensory intensity or unpleasantness implied by each descriptor. Additional cross-modality matches to physically measurable line-length stimuli produced calibration functions used to transform mean handgrip or time-duration responses to each descriptor from units of force or time to common units of line length, referred to as units of relative magnitude.
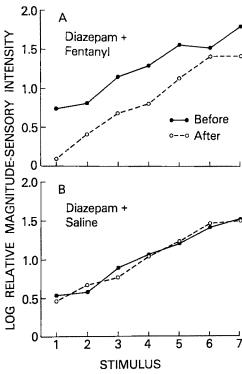
FIG 1. Relative magnitude of patients' verbal judgments of sensory intensity to electrical stimulation of tooth pulp. Responses are shown before (●) and after (○) intravenous administration of 0.11 mg/kg of diazepam with either 0.66 μg/kg of fentanyl (A) (n = 10) or saline placebo (B) (n = 10). Relative magnitude of sensory intensity is shown on ordinate; seven stimuli that increase in equal log steps from pain threshold (mean = 15.7 ± 9.7 [SD] μamp) to pain tolerance (mean = 27.1 ± 14.3 [SD] μamp) are shown on abscissa. Each point is geometric mean of 60 observations.

injections were analyzed by two-way analyses of variance of log response (before/after injection × stimulus) for each drug. As differences in predrug base line responses may contribute to the observed effects, the data for each dimension were analyzed also by two-way analyses of covariance of the difference between the log response before and after drug administration (fentanyl effect/saline effect × stimulus) with the base line as a covariate.

Sensory intensity responses were reduced significantly following the administration of diazepam with fentanyl [F (1, 9) = 8.05, $p < 0.05$] but not after the administration of diazepam with saline [F (1, 9) = 0.024]. A direct statistical comparison of the effects of each drug combination by an analysis of covariance shows that the changes in responses (difference scores) after diazepam with fentanyl also were significantly greater than the response changes after diazepam with saline [F (1, 18) = 8.91, $p < 0.01$]. Thus, the observed effects represent the action of the drug and not the effect of base line level.

Similar effects were observed in a previous study (5) in which fentanyl or saline was administered without a preinjection of diazepam. Sensory intensity responses were reduced significantly after the administration of fentanyl alone but not after saline alone, and the difference between these effects was significant.

Unpleasantness descriptor responses also were quantified by substituting relative magnitudes individually determined for these descriptors. Group mean log unpleasantness responses plotted against the seven tooth pulp stimuli are shown in Fig 2: before and after the administration of diazepam with fentanyl (Fig 2, A) and before and after the administration of diazepam with saline (Fig 2, B).

Unpleasantness responses were unaffected after the administration of diazepam with fentanyl [F (1, 9) = 0.996], but reduced significantly after the administration of diazepam with saline [F (1, 9) = 8.65, $p <$ 0.02]. However, an analysis of covariance showed that the change in response (difference scores) observed
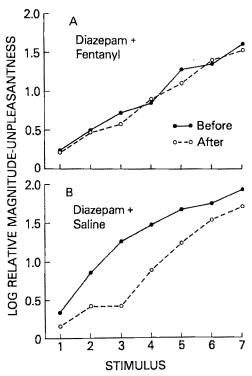
Fig 2. Relative magnitudes of patients' verbal judgments of unpleasantness to electrical stimulation of the tooth pulp. Responses are shown before (●) and after (○) intravenous administration of 0.11 mg/kg of diazepam with either 0.66 μg/kg of fentanyl (A) (n = 10) or saline placebo (B) (n = 10). Relative magnitude of unpleasantness is shown on ordinate; seven stimuli that increase in equal log steps from pain threshold (mean = 15.03 ± 7.15 [SD] μamp) to pain tolerance (mean = 27.55 ± 21.64 [SD] μamp) are shown on abscissa. Each point is geometric mean of 60 observations.

after the administration of diazepam with fentanyl was not significantly different from the change found after the administration of diazepam with saline [F (1, 18) = 3.71, $p =$ 0.071]. Although there is a trend for a difference between the results in Fig 2, A and B; the magnitude of the differences shown results partly from differences in base line level. Similar results were also seen in a previous study (5) in which fentanyl and saline were administered without a preinjection of diazepam. Unpleasantness responses were reduced after saline alone but not after fentanyl alone, but the difference between these effects was not statistically significant (5).

Discussion

The intensities of sensations produced by the tooth pulp stimulation were unaltered by diazepam with saline but were reduced significantly following administration of diazepam with fentanyl. The similarity of these results to those in which fentanyl or saline was administered without a preinjection of diazepam suggests that the effects observed for fentanyl do not represent an artifact of detecting an active drug effect. They also support the results of other studies (7-9, 11, 21) that show that diazepam has little, if any, effect on the intensity of pain sensations.

The present results also suggest that diazepam did not appreciably alter unpleasantness ratings of the tooth pulp sensations. Both this and a previous study (5) in which diazepam was not administered showed a nonsignificant trend for a greater reduction in unpleasantness responses after saline than after fentanyl. The addition of diazepam in this study appeared to have no effect on the results of the previous experiment (5). This similarity suggests that diazepam's action at a dose of 0.11 mg/kg in this paradigm is indistinguishable from that of saline. Further studies are needed to determine whether diazepam produces no effect on the unpleasantness of tooth pulp pain, or if it produces a reduction in unpleasantness that is nonadditive with the observed placebo effect. A nonadditive effect would occur, for example, if either manipulation is sufficient to produce a maximal reduction in unpleasantness responses.

The present results provide additional support for the finding that narcotic analgesics produce clinical analgesia in part by reducing the intensity of pain sensations. In addition to analgesic effects observed in this and a previous study (5), we have assessed the effects of fentanyl in five additional experiments and the action of morphine in one study (22, 23, unpublished observations). In every case, sensory intensity

responses were reduced after administration of these narcotic analgesics. These psychophysical results in human subjects and recent evidence from behavioral and physiologic studies in animals (24–26) provide converging lines of evidence that mechanisms of narcotic analgesia include attenuation of the sensory-discriminative aspects of pain perception.

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Effects of Mepivacaine on Adrenergic Neuroeffector Junction of the Isolated Rabbit Aorta

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FUKUDA, S., TSUJI, T., MURAKAWA, T., TAKESHITA, H., AND TODA, N.: Effects of mepivacaine on adrenergic neuroeffector junction of the isolated rabbit aorta. Anesth Analg 1982;61:756–62.

The effect of mepivacaine on adrenergic neuroeffector junction was studied in the isolated rabbit aorta. Mepivacaine, 5×10^{-5} to 5×10^{-4} M, attenuated the contractile response to transmural neural stimulation, the attenuation being greater in the response at high frequency stimulations. The attenuation of the responses by mepivacaine was not prevented by prior application of cocaine. The concentration-response curve for norepinephrine was shifted to the right by mepivacaine, 5×10^{-5} to 2×10^{-3} M. The attenuation of the response to transmural stimulation was greater than that of the response to an equipotent concentration of exogenous norepinephrine. Pretreatment with mepivacaine, 5×10^{-5} to 2×10^{-3} M, protected alpha-adrenoceptors from persistent blockade by phenoxybenzamine in a dose-dependent manner. The contractile response to histamine was not significantly altered by mepivacaine in concentrations up to 5×10^{-4} M. Mepivacaine, 5×10^{-4} and 2×10^{-3} M, decreased the response to high concentrations of KCl. Ca^{2+}-induced contractions in aortic strips previously exposed to Ca^{2+}-free media and depolarized by excess K^+ were significantly inhibited by mepivacaine, 5×10^{-4} and 2×10^{-3} M. It may be concluded that mepivacaine causes vasodilation through an alpha-adrenoceptor antagonism in addition to a sympathetic nerve conduction blockade. High concentrations of mepivacaine appear to interfere with the transmembrane influx of calcium in the vascular smooth muscle.

Key Words: ANESTHETICS, Local: mepivacaine; SYMPATHETIC NERVOUS SYSTEM: local anesthetics; ARTERIES: local anesthetics.

MEPIVACAINE is widely used for all types of infiltration and regional nerve block anesthesia. However, whether mepivacaine constricts (1, 2) or dilates (3–5) the vascular smooth muscle is controversial. Åberg and Dhunér (6) reported that mepivacaine could produce vasodilation in the hind limb of dogs, when the vessels had previously been contracted by an infusion of norepinephrine (NE). In contrast, if vascular tone was decreased by alpha-blockade, mepivacaine decreased the blood flow. According to

Åberg and Whalström (7), mepivacaine produced contractions of the isolated rat portal vein under relaxed conditions, whereas the compound relaxed the portal vein contracted with KCl and NE. It seems that the action of mepivacaine alters depending on the vasomotor tone of vascular smooth muscle. The major way in which neurogenic alterations of vasomotor tone are produced is undoubtedly through changes in the activity of sympathetic adrenergic nerves innervating the vascular wall (8). Thus, the present study was undertaken to clarify the effect of mepivacaine on the response of isolated rabbit aortas to stimulation of sympathetic nerves and exogenously applied agonists, including NE, epinephrine, histamine, and KCl, and to evaluate the actions of this compound on the adrenergic neuroeffector junction in the blood vessel wall.

Methods

Male albino rabbits, weighing 1.8 to 2.5 kg each, anesthetized with ether, were killed by bleeding from the carotid arteries, and the thoracic aorta was iso-

lated. The aorta was helically cut into strips approximately 25 mm long. The thoracic aorta was used for obtaining the dose-response curve for NE, KCl, epinephrine, and histamine. The specimen was fixed vertically between hooks, under a resting tension of 2 g, in a muscle bath (20 ml capacity) containing the nutrient solution. Hooks anchoring the upper end of the strips were connected to the lever of a force-displacement transducer (Nihonkoden Kogyo Co., Tokyo, Japan). The solution was maintained at 37 ± 0.5°C and aerated with a mixture of 95% O_2 and 5% CO_2. The composition of the nutrient solution was as follows (mM): Na^+, 143.0; K^+, 5.9; Ca^{2+}, 2.5; Mg^{2+}, 1.2; Cl^-, 153.9; HCO_3^-, 25.0; SO_4^{2-}, 1.2; $H_2PO_4^-$, 1.2; dextrose, 10.0. The pH of the solution was 7.35 to 7.40. Before the start of experiments, the preparations were equilibrated for 60 to 90 minutes, during which time the bathing solution was replaced every 10 minutes.

The aortic strips were placed between stimulating electrodes of a platinum plate (5x10 mm) (9). The gaps between the electrodes and strips were wide enough to allow for undisturbed contraction, and yet sufficiently narrow to permit effective stimulation of intramural nerve terminals. The preparations were transmurally stimulated by 0.3-msec square pulses with supramaximum intensity (20 V) at frequencies of 2, 5, and 20/sec. The number of electrical pulses was kept constant (200 pulses) by changing the period of stimulation (100, 40, and 10 seconds for frequencies of 2, 5, and 20/sec, respectively). Transmural stimulation was applied repeatedly until steady responses were obtained. In five aortic strips, the effect of mepivacaine, 10^{-4} M, on the contractile responses to transmural stimulation in the presence of cocaine, 3 × 10^{-6} M, was tested. The effects of bretylium, 2 × 10^{-5} M or phentolamine, 10^{-6} M, on the contractile response to transmural stimulation were tested in four strips of each.

Norepinephrine, epinephrine, KCl, and histamine were applied directly to the bathing medium in cumulative concentrations. After 20-minute exposure of preparations to test drugs, the dose-response relationships of NE, epinephrine, KCl, and histamine and the contractile responses to transmural stimulation were obtained. The tension developed by NE, 5 × 10^{-5} M; epinephrine, 5 × 10^{-5} M; KCl, 5 × 10^{-2} M; or histamine, 2 × 10^{-4} M, in control media was taken as 100%.

To test the protection by mepivacaine from phenoxybenzamine-induced persistent blockade of alpha-adrenoceptors, the complete NE dose-response curve was obtained first. In the nontreated series of experiments, preparations were left for 30 minutes in the
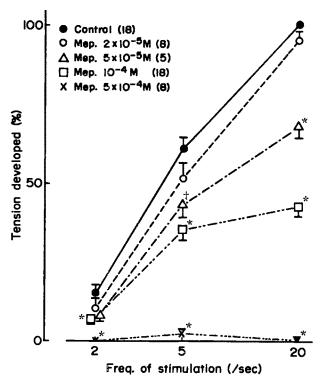
FIG 1. Modification by mepivacaine (Mep) of contractile response to transmural stimulation. Response at frequency of 20/sec in control media was taken as 100%; mean absolute value of tension was 0.60 ± 0.05 g (n = 18). Values in parentheses indicate number of preparations used. *$p < 0.001$; †$p < 0.05$ for differences from control values. Mepivacaine attenuated tension developed at higher frequencies to greater extent.

TABLE 1

Modification of Mepivacaine-Induced Attenuation of Contractile Response to Transmural Stimulation by Cocaine*

Solution	Frequencies of stimulation	
	5/sec	20/sec
	g	
Control	0.36 ± 0.06 (100)	0.59 ± 0.09 (100)
Mepivacaine, 10^{-4} M	0.23 ± 0.08 (57)†	0.21 ± 0.07 (33)†
Control	0.33 ± 0.04	0.52 ± 0.08
Cocaine, 3 × 10^{-6} M	0.73 ± 0.13 (100)†	1.09 ± 0.12 (100)†
Mepivacaine, 10^{-4} M	0.39 ± 0.14 (49)‡	0.26 ± 0.09 (22)†‡

* Values are means ± SEM. In all cases number of preparations is 5. Values in parentheses represent percentage of the tension (values obtained before mepivacaine were taken as 100%).

† $p < 0.05$ compared with data for control group, paired t-test.

‡ $p < 0.05$ compared with data for cocaine group, paired t-test.
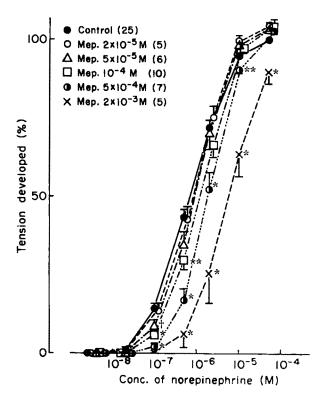
FIG 2. Alterations by mepivacaine (Mep) in dose-response relationship of norepinephrine (NE). Contractile response to NE, 5×10^{-5} M, in control media was taken as 100%; mean absolute value of tension was 2.48 ± 0.12 g (n = 25). $^*p < 0.001$; $^{**}p < 0.01$; $\dagger p < 0.05$ for differences from control values. Mepivacaine shifted dose-response curve for NE to right in dose-dependent manner.

medium without mepivacaine and then exposed for 30 minutes to phenoxybenzamine, 2×10^{-8} M. The preparations were washed with fresh nutrient solutions and equilibrated for 60 minutes. The dose-response curve for NE was then obtained. In the treated series of experiments, preparations were pretreated for 30 minutes with mepivacaine in various concentrations and for another 30 minutes with phenoxybenzamine, 2×10^{-8} M, in the presence of mepivacaine. After the treated drugs were discarded, the dose-response curve for NE was obtained as was in nontreated preparations.

Studies on the interaction between mepivacaine and Ca^{2+} were carried out as follows. The contractile response to KCl, 3×10^{-2} M, was obtained in normal solutions, and the strips were repeatedly washed and equilibrated for 60 minutes. Then, the preparations were exposed for 60 minutes to Ca^{2+}-free media, during which time the medium was replaced twice every 20 minutes. Ten minutes after the addition of KCl (3×10^{-2} M) to the Ca^{2+}-free media, Ca^{2+} in a concentration of 2.5 mM was added. When Ca^{2+}-induced contractions stabilized, additional Ca^{2+} (2.5 and 5.0 mM) was applied. Preparations were treated for 20 minutes with mepivacaine before the addition of KCl.

Values presented in the text and figures are mean values $\pm$ SEM. The data were analyzed statistically by the Student's paired or unpaired t-test; $p < 0.05$ was considered to be significant. Drugs used were:

TABLE 2

Effects of Mepivacaine on Median Effective Concentration (ED₅₀s) of Norepinephrine, Histamine, KCl, and Epinephrine*

Mepivacaine concentration	ED₅₀ of:			
	Norepinephrine ($\times 10^{-7}$ M)	Histamine ($\times 10^{-5}$ M)	KCl ($\times 10^{-3}$ M)	Epinephrine ($\times 10^{-7}$ M)
0 (control)	7.5 ± 0.4 (n = 25)	1.2 ± 0.0 (n = 13)	21.6 ± 0.6 (n = 10)	6.7 ± 0.3 (n = 10)
2×10^{-5} M	6.3 ± 0.7 (n = 5)	—	—	—
5×10^{-5} M	$9.8 \pm 1.2\ddagger$ (n = 6)	—	—	—
10^{-4} M	$11.8 \pm 1.7\dagger$ (n = 10)	1.2 ± 0.1 (n = 5)	20.8 ± 0.9 (n = 7)	$9.8 \pm 0.8\dagger$ (n = 5)
5×10^{-4} M	$19.3 \pm 2.7\dagger$ (n = 7)	1.2 ± 0.1 (n = 5)	23.3 ± 0.9 (n = 6)	$12.3 \pm 0.1\dagger$ (n = 5)
2×10^{-3} M	$86.1 \pm 22.0\dagger$ (n = 5)	$4.1 \pm 0.6\dagger$ (n = 6)	—§ (n = 6)	—

* Values are means $\pm$ SEM; n, number of preparations.
† $p < 0.001$ compared with data for control group, unpaired t-test.
‡ $p < 0.05$ compared with data for control group, unpaired t-test.
§ ED₅₀ could not be determined because maximum response was suppressed.
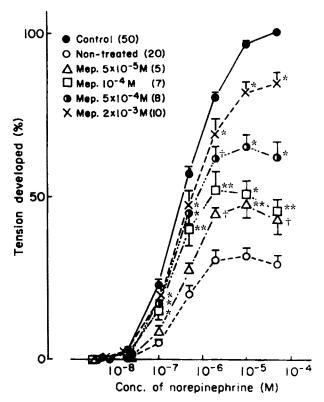
FIG 3. Modification of phenoxybenzamine-induced alpha blockade by prior treatment with mepivacaine (Mep). Contractile response to NE, 5×10^{-5} M, in control media before treatment with mepivacaine and phenoxybenzamine was taken as 100%; mean absolute value of contraction was 2.74 ± 0.09 g (n = 50). Nontreated, Dose-response curve for NE in preparations that were not pretreated with mepivacaine but treated with phenoxybenzamine, 2×10^{-8} M. Mepivacaine 5×10^{-5} to 2 $\times 10^{-3}$ M, dose-response curves for NE in preparations that were pretreated with mepivacaine, 5×10^{-5} to 2×10^{-3} M, then treated with phenoxybenzamine. *$p < 0.001$; **$p < 0.01$; †$p < 0.05$ for differences from nontreated group. Mepivacaine protected alpha-adrenoceptors from phenoxybenzamine in a dose-dependent manner.

mepivacaine hydrochloride (Yoshitomi Pharmaceutical Co.), dl-norepinephrine hydrochloride (Sankyo Co.), histamine hydrochloride (Nakarai Chemical Ltd.), bretylium tosylate (Wellcome Pharmaceutical Co.), phentolamine mesylate (Nippon Ciba-Geigy Ltd.), cocaine hydrochloride (Takeda Pharmaceutical Co.), and phenoxybenzamine hydrochloride (Nakarai Chemical Ltd.).

Results

Treatment with mepivacaine, 2×10^{-5} M, did not alter the response to transmural stimulation. However, mepivacaine at 5×10^{-5} M significantly attenuated the response to the stimulation at 5 and 20/sec.

Mepivacaine at 10^{-4} M significantly attenuated the response to the stimulation at all frequencies used, the attenuation being greater in the response at high frequencies. A further increase in the concentration to 5×10^{-4} M abolished the response to stimulation (Fig 1). The inhibition was reversed by repeated washing of preparations. The inhibitory effect of mepivacaine, 10^{-4} M, was not prevented by treatment with cocaine, 3×10^{-6} M (Table 1). The tension of aortic strips was not altered by mepivacaine in concentrations up to 2×10^{-3} M. Contractile responses to transmural stimulation were abolished by treatment for 20 minutes with bretylium, 2×10^{-5} M, or phentolamine, 10^{-6} M, in all of four aortic strips of each.

The concentration-contractile response curve for NE was shifted to the right by mepivacaine (5×10^{-5} to 2×10^{-3} M) in a dose-dependent manner (Fig 2, Table 2). The inhibitory effect was reversed by repeated washing of the preparations. Concentrations of NE sufficient to produce the same magnitude of contractions as that with transmural stimulation at a
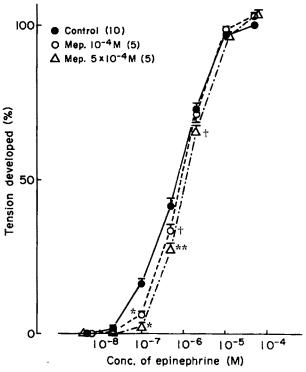
FIG 4. Alterations by mepivacaine (Mep) in dose-response relationship of epinephrine. Contractile response to epinephrine, 5×10^{-5} M, in control media was taken as 100%; mean absolute value of tension was 2.05 ± 0.08 g (n = 10). *$p < 0.001$; **$p < 0.01$; †$p < 0.05$ for differences from control values. Mepivacaine shifted dose-response curve for epinephrine to right at 10^{-4} and 5×10^{-4} M.

frequency of 20/sec were 3.4×10^{-7} M. Mepivacaine, 5×10^{-5}, 10^{-4}, and 5×10^{-4} M, reduced the response to this concentration of NE by $5.1\% \pm 3.3\%$ (N = 6), $11.0\% \pm 2.9\%$ (N = 10), and $24.8\% \pm 4.5\%$ (N = 7), respectively, whereas inhibitions of the responses to transmural stimulation at 20/sec by these concentrations of mepivacaine averaged $32.0\% \pm 4.2\%$ (N = 5), $57.3\% \pm 3.3\%$ (N = 18), and $99.8\% \pm 0.2\%$ (N = 8), respectively.

Treatment with phenoxybenzamine, 2×10^{-8} M, markedly attenuated the contractile response to NE (Fig 3, compare solid and open circles). Prior treatment with mepivacaine prevented the inhibitory effect of phenoxybenzamine (Fig 3, compare nontreated and mepivacaine-treated preparations). The higher concentration of mepivacaine, the greater the prevention (Fig 3).

The dose-response curve for epinephrine was shifted to the right by mepivacaine, 10^{-4} and 5×10^{-4} M (Fig 4, Table 2). The inhibition estimated from the curve of the epinephrine $(3.9 \times 10^{-7}$ M)-induced contraction by mepivacaine, 5×10^{-4} M, was $14.6\% \pm 1.0\%$ (N = 5). Mepivacaine in concentrations lower than 10^{-4} M did not alter the dose-response curve for KCl, but at 5×10^{-4} M, reduced the contraction induced by high concentrations of KCl (30 to 50 mM). The greater attenuation was attained after treatment with 2×10^{-3} M mepivacaine (Fig 5). Treatment with mepivacaine at 2×10^{-3} M shifted the dose-contractile response curve for histamine to the right (Fig 6) and significantly increased the median effective concentration of histamine (Table 2).

Contractions induced by Ca^{2+} (2.5 mM) in aortic strips previously exposed for 60 minutes to Ca^{2+}-free media and depolarized by excess K^+ were inhibited by mepivacaine at 5×10^{-4} and 2×10^{-3} M in a dose-dependent manner. The inhibitory effect of mepivacaine was overcome by increasing external Ca^{2+} to 5.0 and 7.5 mM (Fig 7).

Discussion

The contractile response of isolated rabbit aortas to transmural electrical stimulation under experimental condition used in the present study is considered to result from NE released by excitation of adrenergic nerves, as the responses were abolished by an alpha-adrenoceptor blocking agent (phentolamine), an adrenergic neuron blocking agent (bretylium), or tetrodotoxin in the present and previous studies (9–11). Mepivacaine attenuated the responses to transmural neural stimulation and to exogenously applied NE in a dose-dependent manner. Bevan and Su (12) have
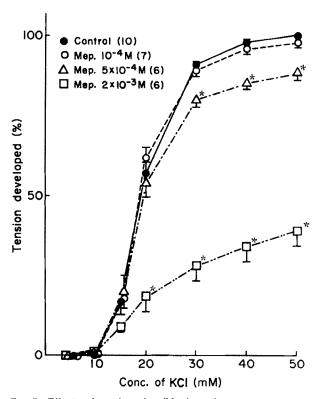
FIG 5. Effects of mepivacaine (Mep) on dose-response curve for potassium chloride (KCl). Contractile response to KCl, 5×10^{-2} M, in control media was taken as 100%; mean absolute value of tension was 2.39 ± 0.08 g (n = 10). *p < 0.001 for differences from control values. Mepivacaine in concentrations lower than 10^{-4} M did not alter response to KCl.

postulated that a uniform distribution of exogenous NE and nonuniform (high concentration close to nerve terminals but the further the distance from the nerves, the less the concentration of NE) distribution of neurogenic NE exist throughout the medium. When equal responses to neurogenic and exogenous NE are induced, the concentration at the nerve terminals of neurogenic NE must be higher than that of the exogenous NE. Thus, well known alpha-adrenoceptor blocking agents like phentolamine or phenoxybenzamine reduce the response to exogenous NE more effectively than the response to adrenergic nerve stimulation (12). In the present study, however, the attenuation of the response to adrenergic nerve stimulation by mepivacaine, 5×10^{-5} to 5×10^{-4} M, was greater than that of the response to an equipotent concentration of exogenous NE. Therefore, it may be concluded that mepivacaine interferes with the release of NE from adrenergic nerves in addition to interference with the action of NE on alpha-adrenoceptors.

The interference with the release of NE may be caused either by a bretylium-like action or by a
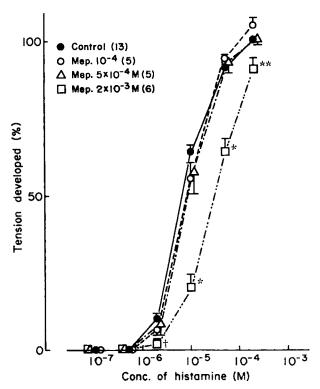
FIG 6. Effects of mepivacaine (Mep) on dose-response curve for histamine. Contractile response to histamine, 2×10^{-4} M, in control media was taken as 100%; mean absolute value of tension was 2.54 ± 0.13 g (n = 13). $*p < 0.001$; $**p < 0.01$; $\dagger p < 0.05$ for differences from control values. Mepivacaine in concentrations less than 5×10^{-4} M did not alter response to histamine.

blockade of nerve conduction. In the present study, prior application of cocaine in a concentration sufficient to prevent the inhibitory effect of bretylium on the release of NE (13) did not prevent mepivacaine-induced attenuation. In addition, the response to high frequencies of transmural stimulation was attenuated by mepivacaine to a greater extent. Similar results were obtained with lidocaine (10). Such an uneven effectiveness may be related to reduced excitability and impaired conduction of nerves by local anesthetics. These findings suggest that mepivacaine attenuates the contractile response to transmural stimulation due to nerve conduction blockade rather than to a bretylium-like effect.

The dose-response curve for NE in rabbit aortic strips was shifted to the right by mepivacaine in concentrations insufficient to reduce the contractile response to KCl and histamine. Furthermore, treatment of aortic strips with mepivacaine effectively protected alpha-adrenoceptors from persistent blockade of phenoxybenzamine. Only blocking agents of a competitive type are effective in such a receptor

protection (14). These findings suggest that mepivacaine reversibly and competitively antagonizes alpha-adrenoceptors.

High concentrations of mepivacaine attenuated the response to KCl or to Ca^{2+} in aortic strips previously exposed to Ca^{2+}-free media. High concentrations of K^+ releases NE from the vascular wall (15). The attenuation of Ca^{2+}-induced contractions by mepivacaine was reversed by excess Ca^{2+}. Thus, it seems likely that the influx of Ca^{2+} across aortic cell membrane is inhibited by high concentrations of mepivacaine. Åberg and Andersson (16) reported that high concentrations of mepivacaine relaxed rat portal vein contracted by NE and the relaxing action of mepivacaine was counteracted by Ca^{2+}. However, it must be emphasized that the alpha-adrenoceptor antagonistic action is more evident in low concentrations of mepivacaine than is the Ca^{2+} antagonistic action.

The addition of epinephrine (1:200,000) to local
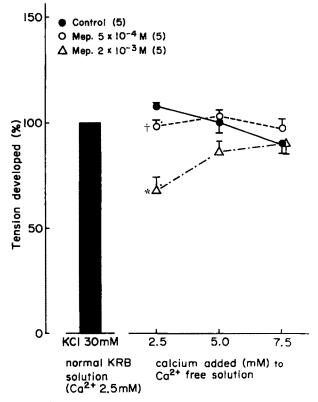
FIG 7. Effect of mepivacaine (Mep) on calcium-induced contractions in preparations exposed to Ca^{2+}-free media containing excess KCl (3×10^{-2} M). Contractile response to KCl, 3×10^{-2} M, in normal solutions (Ca^{2-} 2.5 mM) was taken as 100%; mean absolute value of tension was 2.22 ± 0.07 g (n = 15). $*p < 0.001$; $\dagger p < 0.05$ for differences from control values. Calcium (2.5 mM)-induced contraction was attenuated by high concentrations of mepivacaine. Excess calcium (5.0 and 7.5 mM) restored contraction.

anesthetics prolongs the duration of anesthesia, mainly due to vasoconstriction and retarded absorption (17, 18). The minimum concentration of mepivacaine sufficient to inhibit significantly the sensory or motor nerve conduction has not been reported, but is probably approximately 5×10^{-4} M, because intrinsic anesthetic potency of mepivacaine in vitro is approximately half the potency of lidocaine, and minimum concentration of lidocaine sufficient to depress significantly the action potential amplitude in an isolated sciatic nerve preparation is 2.5×10^{-4} M (18). If 1% mepivacaine solution containing epinephrine (1:200,000) epidurally administered is diluted to a concentration of 5×10^{-4} M sufficient to block the sensory and motor nerve root, the concentration is added epinephrine would be 3.9×10^{-7} M, assuming that the amine is equally diluted and is not metabolized. In the present study, mepivacaine, 5×10^{-4} M, inhibited the contraction of aortic strips induced by epinephrine, 3.9×10^{-7} M, only by 14.6% (Fig 4). This suggests that epinephrine in this concentration retains the ability to cause contraction of arterial smooth muscle despite the presence of the alpha-adrenoceptor antagonism by mepivacaine.

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Thiopental Suppression of Neurons of the Nucleus Reticularis Gigantocellularis of the Cat

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The effects of sodium thiopental on the single-unit activity of cells in the nucleus reticularis gigantocellularis (NRGC) were examined in decerebrated cats. Only cells in the NRGC that responded exclusively to electrical stimulation of A-delta fibers (noxious stimulation) in the superficial radial nerve were studied. Sodium thiopental caused a significant, dose-dependent suppression of spontaneous and evoked neuronal activity of cells in the NRGC. Spontaneous activity was suppressed by 66% and 98% after intravenous administration of sodium thiopental, 2.5 mg/kg and 5.0 mg/kg, respectively. Evoked activity was suppressed by 65% and 79%. These findings, when added to previous reports of the suppressive effects of nitrous oxide, morphine sulfate, ketamine hydrochloride, and halothane, suggest the involvement of the NRGC in nociception and provide evidence that sodium thiopental significantly modifies the neuronal message about a noxious stimulus as recorded at the level of the NRGC.

Key Words: ANESTHETICS, Intravenous: thiopental; BRAIN: nucleus reticularis gigantocellularis.

FOR DECADES the reticular formation has been considered to be a site of action for anesthetic agents. The nucleus reticularis gigantocellularis (NRGC), located at the caudal end of the reticular formation, has recently been identified as an important locus for the transmission of nociceptive information from the spinal cord to higher brain centers, and it may also·relay descending information to the spinal cord (1). Burton (2) reported that cells in the NRGC were activated when noxious stimuli were presented to their peripheral receptive fields. Bowsher et al (3) proposed that cells in the NRGC form a relay for somatic impulses between the spinal cord and higher brain areas. Casey (4, 5) demonstrated that cells in the NRGC, when activated by electrical stimulation of the superficial radial nerve, had an increased neuronal activity which was associated with escape behavior in trained cats. Responses of cells in the NRGC to various types of stimulation (including non-noxious stimuli) have been reported (6, 7), but it is agreed that many cells in the NRGC respond exclusively or maximally to noxious stimulation of peripheral receptive fields.

Many reports suggest that anesthetic agents selectively suppress the activity of central nervous system neurons which are activated by noxious stimuli. A selective effect of anesthetic and analgesic agents on spinal cord neuronal activity has been associated with noxious stimuli. Anesthetic agents such as nitrous oxide, morphine sulfate, ketamine hydrochloride, and halothane have been reported (8-11) to suppress the neuronal activity of cells in the NRGC. This study was undertaken to examine the effect of sodium thiopental on noxiously evoked single-unit activity of NRGC neurons. Such changes would provide support for the theory that part of the anesthetic effect of sodium thiopental is due to its ability to modify neuronal signals that can be recorded in the NRGC.

Methods

Thirty cats of either sex, weighing 2.5 to 4.5 kg each, were used in this study. Under halothane-nitrous oxide-oxygen anesthesia, a tracheostomy was performed, and a femoral artery and vein were cannulated for direct arterial blood pressure recording and intravenous fluid and drug administration. After mounting the head in a Horsley-Clarke stereotaxic apparatus, electrolytic lesions were made in the mid-

brain reticular formation for supracollicular decerebration. These lesions were placed according to the stereotaxic atlas of Snider and Niemer (12). General anesthesia was then discontinued (average duration was 60 minutes), and the lungs were artificially ventilated with 100% O_2. End-tidal CO_2 was maintained at 30 to 36 torr as measured by an infrared gas analyzer. A pneumothorax was made to reduce the movement of the brainstem due to ventilation. Neuronal recordings were not started until at least 2 hours after the end of anesthesia.

An intravenous infusion of lactated Ringer's solution with gallamine triethiodide (0.1%) was administered at a rate of 4 to 8 ml/kg/hr. Systolic arterial blood pressure was maintained at greater than 90 torr by administering volumes of lactated Ringer's solution as necessary. If the blood pressure decreased to less than 90 torr, the experiment was terminated. Systolic arterial pressure never increased to greater than 190 torr. Rectal temperature was maintained at 37.0 ± 1.0°C by a servo-controlled water mattress and infrared heating lamps.

The superficial radial nerve was exposed and prepared for the placement of two pairs of silver bipolar electrodes: the proximal pair for stimulating and the distal pair for recording the compound action potentials. A paraffin oil pool was made to protect the nerve from drying; the temperature of the paraffin oil was maintained at 37.0 ± 0.5°C by a thermostatically controlled heating device.

The threshold intensity and the intensity required for maximum activation of the A-beta and A-delta components of the compound action potential of the superficial radial nerve were determined. Supramaximal stimulation of A-beta and A-delta fibers was used to evaluate the response characteristics of each NRGC neuron.

The snout of the animal was tilted 45° downward from the horizontal plane. Following suboccipital craniotomy, a tungsten microelectrode with a 1- to 2-μ exposed tip (impedance 9 to 14 Mohm at 1000 Hz) was inserted at an angle of 25° from the vertical, 1.0 to 2.5 mm rostral and lateral to the obex, to a depth of 2000 to 5000 μ from the dorsal surface. The microelectrode insertion was performed by a hydraulic micromanipulator.

As the microelectrode was advanced into the area of the NRGC, to record extracellularly from single neurons, the contralateral superficial radial nerve was electrically stimulated. The stimulation consisted of a train of 10 pulses, each 1 msec in duration at a frequency of 100 Hz. These stimulus parameters were

found, in previous studies, to be optimal for the activation of the NRGC neurons.

When activity of a single neuron with an adequate signal-to-noise ratio was isolated, its response to electrical stimulation of the superficial radial nerve at A-beta and A-delta intensities was evaluated. Only cells that responded exclusively to A-delta fiber (i.e., noxious) stimulation were studied. During recording of the neuronal activity of the NRGC, the electrical stimulus was repeated every 60 seconds at twice maximal voltage for activation of A-delta fibers. The compound action potential was continuously monitored on a cathode-ray oscilloscope.

Following control studies, sodium thiopental (2.5 or 5.0 mg/kg) was administered intravenously over a period of 60 seconds. Spontaneous and stimulus-evoked activity of a single NRGC neuron were monitored and recorded continuously until they recovered to control values. Drug studies were performed on only one neuron in each animal to eliminate accumulation of drug effects.

The neuronal impulses were amplified by a differential AC amplifier, displayed on a cathode-ray oscilloscope, monitored by a sound system, and discriminated by an amplitude discriminator. The instantaneous firing frequency was traced on a polygraph and the amplified neuronal impulses and stimulus markers were recorded on magnetic tape for later computer analysis.

Data recorded on magnetic tape were analyzed with the aid of a digital computer (DEC PDP 11/40). The spontaneous activity was averaged for 30 seconds, immediately before nerve stimulation. The evoked activity was averaged following electrical stimulation of the superficial radial nerve. The stimulus usually produced a period of activation that lasted for 1 to 2 seconds. The duration of the activation during control studies for each neuron was used as the time period for averaging for that neuron. The evoked activity was considered to be any increase in neuronal firing frequency that was greater than the mean base line spontaneous rate. The statistical significance of the data was assessed using a paired t-test for changes from control values and Student's t-test for differences between dosages.

Results

Recordings were obtained from single neurons (n = 30) located within the NRGC. All of the cells responded exclusively to A-delta fiber stimulation of the superficial radial nerve with a burst of neuronal

activity lasting for several seconds which then returned to the prestimulus level of spontaneous activity.

Typical changes in the spontaneous and evoked neuronal activity of an NRGC neuron before and after the administration of sodium thiopental (2.5 and 5.0 mg/kg) are shown in the Figure.

The effect of sodium thiopental (2.5 and 5.0 mg/kg) on the mean spontaneous activity of all cells studied is shown in Table 1. All cells were maximally suppressed by sodium thiopental at both dosages within 5 minutes after intravenous administration, and the effect appeared to be dose dependent.

The effect of sodium thiopental (2.5 and 5.0 mg/kg) on mean evoked activity is shown in Table 2. All cells were maximally suppressed by sodium thiopental, at both doses, within 5 minutes after intravenous administration.

The activity of a majority of the neurons returned to control values at approximately 30 and 50 minutes after sodium thiopental, 2.5 and 5.0 mg/kg, respectively. The remaining neurons returned to within 80% of control values at that same time.
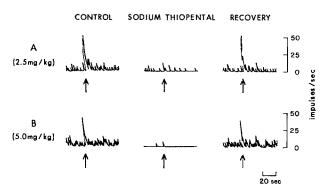
FIGURE. Example of polygraph tracings of instantaneous firing frequency (impulses/second) of single-unit activity in nucleus reticularis gigantocellularis during control period (left), 3 minutes after intravenous administration of sodium thiopental (middle), and during recovery (right). Arrows indicate time of occurrence of superficial radial nerve stimulation.

TABLE 1

Effect of Sodium Thiopental on Mean Spontaneous Activity of Single Neurons in Nucleus Reticularis Gigantocellularis*

Sodium thiopental	Control	Firing rate at maximum suppression	Maximum % suppression from control values
		impulses/sec	
2.5 mg/kg (n = 15)	6.0 ± 2.8	2.0 ± 0.7†	66.6 ± 11.1
5.0 mg/kg (n = 15)	6.5 ± 2.0	0.1 ± 0.1†	98.3 ± 1.1‡

* Values are means ± SE.
† Significantly different from control values, $p < 0.01$ (paired t-test).
‡ Significantly different from 2.5-mg dose, $p < 0.01$ (Student's t-test).

TABLE 2

Effect of Sodium Thiopental on Mean Evoked Activity of Single Neurons in Nucleus Reticularis Gigantocellularis*

Sodium thiopental	Control	Firing rate at maximum suppression	Maximum % suppression from control values
		impulses/sec	
2.5 mg/kg (n = 15)	42.6 ± 3.2	14.8 ± 2.6†	65.2 ± 6.2
5.0 mg/kg (n = 15)	43.3 ± 2.8	8.9 ± 2.8†	79.4 ± 6.5

* Values are means ± SE.
† Significantly different from control values, $p < 0.001$ (paired t-test).

Discussion

Research conducted in the 1940s and 1950s established both the importance of the reticular formation in the control and maintenance of consciousness and the sensitivity of that system to suppression by anesthetic agents. Although we now know that anesthetics have multiple sites of action, the reticular formation is still considered to be an important site of action for anesthetics. Recent research has established that specific loci in the reticular formation are important for the detection or alleviation of pain. A recent review (1) summarizes currently held ideas about such areas and indicates that the NRGC is likely to play an important role in the transmission of information about noxious events at the periphery. For example, anatomic studies have revealed that spinoreticular pathways have direct primary nociceptive afferent projections to the NRGC.

It has been shown by Casey (13) that a majority of the NRGC neurons respond exclusively to noxious stimulation of their receptive fields. Guilbaud et al (14) applied intra-arterial injections of bradykinin (a pain-producing substance in humans) as a noxious stimulus and observed activation of neurons in the NRGC. The adequate electrical stimulus for altering the NRGC activity has been shown to be stimulation greater than A-delta threshold (13, 15), an intensity established by Collins et al (16) as necessary to evoke a sensation of pain in humans. Casey (5) demonstrated that electrical stimulation of the NRGC elicits escape and natural pain behavior in trained cats and proposed a hypothesis that the region of the NRGC is an integral part of central pain sensory mechanisms.

While studies of the anatomy and physiology of the NRGC have continued, some investigators have tried to substantiate the function of the NRGC through pharmacologic studies. Spencer et al (8) reported that neuronal activity of cells in the NRGC, activated by noxious stimulation of peripheral nerves,

was suppressed by nitrous oxide. Using similar electrophysiologic methods, ketamine hydrochloride (9), halothane (10), and morphine sulfate (11) have also been reported to suppress the activity of cells in the NRGC. The above cited reports indicate that anesthetic agents suppress noxiously evoked neuronal activity of the NRGC and that the suppression is greater than that seen in the spinal cord.

Behavioral studies by Takagi et al (17, 18), in which morphine or enkephalin was microinjected into the NRGC, further support the involvement of the NRGC in the production of analgesia. These studies demonstrated that such injections could produce analgesia in awake rats.

The results of the present study substantiate previous work which has revealed that anesthetic and analgesic agents are capable of suppressing neuronal activity recorded at the NRGC. The importance of the suppression of noxiously evoked activity in the present study needs to be emphasized. A-delta stimulation is recognized as being painful in humans and nocifensive in animals. Suppression of noxiously evoked activity to the degree seen in the present study indicates that the "neuronal message" associated with the noxious stimulus is severely restricted by the time it reaches the NRGC. This suppression is probably not due to the drug action at a single site (i.e., NRGC), as we know that the barbiturates can reduce noxiously evoked activity at the level of the spinal cord (19). It is apparent, however, that the degree of suppression measured at the NRGC is greater than that seen in the spinal cord.

The afferent role of the reticular formation has been thought of as one of activation, i.e., the reticular activating system "alerts" higher brain regions. Perhaps the drug-induced suppression of such activity, as seen in the present study, functions to decrease the "alerting signals" which would otherwise reach higher areas of the central nervous system. Such changes would be likely to decrease the awareness or sensation of noxious events at the periphery.

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Neuromuscular Blocking Effects of Tobramycin, Gentamicin, and Cefazolin

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LIPPMANN, M., YANG, E., AU, E., AND LEE, C.: Neuromuscular blocking effects of tobramycin, gentamicin, and cefazolin. Anesth Analg 1982;61:767-70.

Forty patients (A.S.A. class I or II), 18 to 75 years of age, who were undergoing elective surgery were studied to determine the clinical and subclinical neuromuscular blocking effects of two antibiotics, tobramycin and gentamicin and to compare these effects with those produced by cefazolin, an aminoglycoside not known to produce paralysis. Patients were prospectively and randomly assigned in approximately equal numbers to one of four groups: group A received 1 mg/kg of tobramycin; group B, 1 mg/kg of gentamicin; group C, 500 mg of cefazolin; or group D, control (no antibiotic). Antibiotics were administered intravenously 45 minutes immediately preceding the study. The ulnar nerve was stimulated supramaximally and neuromuscular function was measured electromyographically. Anesthesia was induced with thiopental, 4 mg/kg IV, and maintained with endotracheal enflurane 1.0% to 1.5% (inspired) and N_2O-O_2 (2 L:1 L) after intubation. Succinylcholine (1 mg/kg) was administered after induction of anesthesia and the magnitude and duration of neuromuscular block monitored. d-Tubocurarine (0.1 mg/kg) was given 5 to 10 minutes after full recovery from succinylcholine and repeated as required. At the end of the operation, atropine, 0.02 mg/kg, and neostigmine, 0.4 mg/kg, were used to reverse the block. Base line neuromuscular data, duration of block of succinylcholine, and potency, duration of block, recovery rate, train-of-four fade, tetanic trend, response to double stimuli, post-tetanic effect, and reversibility of the subsequent d-tubocurarine-induced neuromuscular block were not significantly different ($p < 0.01$) between any two groups. Tobramycin, gentamicin, and cefazolin, in recommended single doses, lack clinical neuromuscular blocking and subclinical relaxant-potentiating effects.

Key Words: ANTIBIOTICS: tobramycin, gentamicin, cefazolin.

THE NEUROMUSCULAR blocking effects of antibiotics and the high mortality associated with accidental paralysis induced by antibiotics are well known (1, 2). Accidental paralysis has been induced clinically by 11 of 21 antibiotics known to cause neuromuscular block.

Pittinger and Adamson (3) have classified neuromuscular blocking antibiotics as: (a) aminoglycosides—neomycin, streptomycin, etc.; (b) polypeptides—polymyxins (A, B, E); (c) tetracyclines; (d) other—clindamycin, lincomycin.

The neuromuscular blocking effects of the aminoglycosides, especially neomycin, have been well studied. The mechanism of action of neomycin includes prejunctional impairment of calcium influx and acetylcholine output together with postjunctional decrease in sensitivity to acetylcholine (4). It has been theorized that neomycin competes with calcium ions at the motor nerve terminal.

Gentamicin and tobramycin, both aminoglycosides, are known to possess neuromuscular blocking effects in animals when given at high doses (5, 6). However, their neuromuscular effects have not been studied, compared, and reported in humans. On the other hand, no clinically significant neuromuscular blocking effects have been observed with cefazolin.

Antibiotic-induced neuromuscular blocks, especially the subclinical blocking effects, are difficult to ascertain. Subclinical effects can be demonstrated on the basis of changes in sensitivity to neuromuscular blocking agents or on the basis of interactions with other drugs affecting the neuromuscular junction. The following parameters of increased sensitivity permit detection of neuromuscular block before the single twitch is depressed: half-refractory period of neuromuscular transmission, train-of-four, and tetanic stimulation. Subclinical effects also may be revealed

by potentiating interactions between anesthetics and muscle relaxants.

Methods and Materials

This study of 40 patients (A.S.A. class I or II) who were undergoing elective bowel, abdominal, chest, or orthopaedic operations, was approved by the Human Subjects Committee. Included were both men and women, 18 through 75 years of age, who gave written consent. Patients were excluded if they were pregnant, had vestibular or hearing dysfunction, were receiving diuretics or any antibiotics within 4 days before the study, or had allergies to tobramycin, gentamicin, or cefazolin.

Patients were assigned randomly in approximately equal numbers to one of four groups: patients in group A received 1 mg/kg of tobramycin; those in group B, 1 mg/kg of gentamicin; those in group C, 500 mg of cefazolin; patients in group D served as control patients and received no antibiotic. All antibiotics were administered by intravenous drip over the 45-minute period immediately preceding the study.

Anesthesia was induced with sodium thiopental, 4 to 5 mg/kg IV, and was maintained with enflurane 1.0% to 1.5% (inspired) and N_2O-O_2 (2 L:1 L) after tracheal intubation. Ventilation was controlled with a ventilator at approximately 10 ml/kg, 10 times per minute.

The thumb twitch in response to ulnar nerve stimulation was monitored. The stimulation consisted of a single supramaximal stimulus at 0.1 Hz, train-of-four stimuli at 2 Hz at appropriate times, and paired stimuli 3 msec apart followed by a tetanic stimuli of 50 Hz of 5 seconds duration before administration of d-tubocurarine and again at 50% recovery of twitch. The thumb twitch was quantified electromyographically [7] and recorded. Succinylcholine (1 mg/kg) was administered and its effect monitored. Five to 10 minutes after full recovery from the succinylcholine, each patient was given the first dose of d-tubocurarine (0.1 mg/kg). Subsequent doses of 0.1 mg/kg were given until greater than 60% suppression of the neurally evoked electromyographic response was achieved. The neuromuscular response to each dose of d-tubocurarine and the time course of the block produced by succinylcholine and d-tubocurarine were quantified and compared among groups (t-tests). This quantification was performed not to determine how valid d-tubocurarine dose-response curves were, but to determine the effect of d-tubocurarine in patients receiving antibiotics after the administration of suc-

cinylcholine. When twitch recovery reached 50%, responses to train-of-four stimuli (8) and tetanic responses were determined. At the end of the operation, atropine, 0.02 mg/kg, and neostigmine, 0.04 mg/kg, were administered to reverse the neuromuscular block. ED_{50} of d-tubocurarine was estimated on log-probit paper.

The means for all variables were compiled for each drug and were analyzed simultaneously for variance (ANOVA); $p < 0.01$ was considered statistically significant.

Results

The responses of the patients receiving tobramycin, gentamicin, or cefazolin did not differ significantly ($p < 0.01$) from those of the control group (Table). This was true when comparisons were made of the base line neuromuscular data, duration of succinylcholine block, and the potency, duration of block, recovery rate, train-of-four fade at 50% block, tetanic trend, response to double stimuli, post-tetanic effect, and reversibility of the block subsequently induced with d-tubocurarine. There were patients in each group who appeared resistant to d-tubocurarine. Not all patients receiving 0.2 mg/kg of d-tubocurarine produced a neuromuscular block greater than 60%. Two patients, one each in the tobramycin and cefazolin groups, required a third dose of 0.1 mg/kg of d-tubocurarine to produce 60% suppression of the electromyograph. A third patient in the tobramycin group required a fourth dose. There were no problems encountered in reversing the neuromuscular blockade following the administration of neostigmine, although the degree of neuromuscular transmission before neostigmine varied. In summary, gentamicin and tobramycin did not increase the sensitivity to d-tubocurarine nor did cefazolin.

Discussion

Gentamicin and tobramycin are known to possess neuromuscular blocking effects and to block neuromuscular transmission in animals at high doses, but they are considered safer than previously popular aminoglycoside antibiotics. Cefazolin is supposedly even safer from the viewpoint of neuromuscular blocking side effects. Until now, subclinical neuromuscular effects of these three antibiotics and their possible potentiating effects on relaxants have not been ruled out.

Tetanic stimulation involves the application of a supramaximal stimulus for 5 seconds at a frequency

TABLE

Patient Responses to Cefazolin, Gentamicin, and Tobramycin*

Variable	Control	Cefazolin	Gentamicin	Tobramycin	ANOVA p value
% Block dTc, 0.1 mg/kg	42.4 ± 0.06	53.1 ± 0.1	29.3 ± 0.09	30.9 ± 0.01	0.241
% Block dTc, 0.2 mg/kg	82.3 ± 0.07	77.9 ± 0.07	84.1 ± 0.03	70.9 ± 0.01	>0.5
ED_{50} (mg/kg)	0.125 ± 0.02	0.113 ± 0.018	0.129 ± 0.013	0.157 ± 0.028	0.485
T_4/T_1 at 50% dTc block	0.18 ± 0.034	0.217 ± 0.012	0.238 ± 0.037	0.269 ± 0.04	0.270
25%–50% recovery time (min)	18.0 ± 3.55	17.25 ± 2.24	21.80 ± 3.49	18.05 ± 2.84	>0.5
Time for 50% gain following neostigmine	2.67 ± 0.22	2.60 ± 0.4	2.75 ± 0.65	3.24 ± 0.48	>0.5
R_2/R_1 at 50% block	—†	0.447 ± 0.07	0.447 ± 0.07	—	>0.5

* Values are means ± SEM. Mean values of the variables measured together for each antibiotic, together with p values. No statistically significant differences ($p < 0.01$) were observed among the mean values of the variables analyzed. Observed significance level was >0.01 in all cases. Abbreviation used is: dTc, d-tubocurarine.

† — Data not available.

of 50 Hz. Normally, the acetylcholine output is greater than necessary to evoke a propagated response in muscle fibers, and is more than adequate to sustain a propagated response over a wide range of frequencies of stimulation. Therefore, the response to tetanic stimulation does not fade. When the margin of safety is decreased, a decrease in acetylcholine output during repetitive nerve stimulation is manifested by the inability to sustain a response to tetanic stimulation.

The train-of-four is a method for quantitatively measuring the degree of non-depolarizing neuromuscular block. It consists of a series of four supramaximal stimuli applied to the ulnar nerve at a frequency of 2 Hz. Each train-of-four is repeated not more frequently than every 10 seconds. The ratio of the amplitude of the fourth evoked response to the amplitude of the first response in the same train is then determined to assess the degree of neuromuscular block. A high train-of-four ratio or minimal fade of the twitch (i.e., a ratio of 0.7 to 0.9) indicates adequate recovery from a non-depolarizing block, whereas a low train-of-four ratio or maximal fade indicates a good neuromuscular block. A frequency of 2 Hz is used because it is rapid enough to produce significant depletion of the immediately available store of acetylcholine and yet slow enough to prevent facilitation.

During and after tetanic stimulation, there is enhanced mobilization of acetylcholine. Following cessation of tetanic stimulation, there is an increase in the readily releasable fraction of acetylcholine. Thus, in the post-tetanic period the quantal content exceeds that in the pretetanic control period. With a non-depolarizing block, however, the pretetanic twitch is submaximal. With the increased post-tetanic response, a larger number of muscle fibers may be excited by nerve stimulation, causing post-tetanic potentiation (9).

The half-refractory period is the interval in which twin stimuli elicit two unequal responses where $R_2 = \frac{1}{2} R_1$ and is usually approximately 3.3 ± 0.7 (SD) msec in the absence of neuromuscular block (9, 10). The significance of R_2/R_1 is an experimental screening method to determine neuromuscular blocking effects of aminoglycoside antibiotics (11). Muscle relaxants, cholinesterase inhibitors, and neomycin change the refractory period of neuromuscular transmission (12, 13).

Interpretation of our results in light of the above background indicates that tobramycin, gentamicin, and cefazolin in recommended single doses do not induce clinical or subclinical relaxant-potentiating neuromuscular effects, nor do they differ from one another in this respect, to the extent detectable by specific monitoring techniques.

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Comparative Cardiovascular Effects of Midazolam and Thiopental in Healthy Patients

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Midazolam, a water-soluble benzodiazepine that is shorter-acting, more potent, and less irritating to veins than diazepam, has been suggested for use for induction of anesthesia. The cardiovascular effects of an induction-sized dose (0.25 mg/kg) of midazolam in A.S.A. class I or II surgical patients (N = 11) sedated with morphine and N_2O-O_2 were compared in a double-blind fashion with a similar group of patients (N = 9) receiving thiopental (4.0 mg/kg). Consistent with earlier studies, patients given thiopental experienced downward trends from base line in mean arterial pressure, stroke volume, cardiac output, and heart rate; mean right atrial pressure increased slightly, whereas systemic vascular resistance did not change. Induction of anesthesia with midazolam was associated with more gradual and less pronounced hemodynamic alteration; the only significant changes from base line were decreases in mean arterial pressure 5 and 10 minutes after injection. When the two groups were compared, no significant differences were found. Midazolam is, then, as acceptable for induction of anesthesia as thiopental from a hemodynamic point of view in A.S.A. class I and II patients.

Key Words: INDUCTION: anesthesia; HYPNOTICS: benzodiazepines, midazolam; ANESTHETICS, Intravenous: thiopental.

THE NEW BENZODIAZEPINE midazolam—8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]-benzodiazepine—is, as the hydrochloride, water-soluble when injected in an aqueous solution of pH <4.0 (due to an open benzodiazepine ring conformation) but becomes lipid-soluble at physiologic pH (due to ring closure) (1). This structural relationship provides a benzodiazepine that is relatively nonirritating to veins (2) and painless on injection, compared with diazepam (3, 4). Other characteristics of midazolam include induction of sleep in less than 2 minutes after intravenous injection (5), an

excretion half-life of 2 hours with no known active metabolites (6), minimal hemodynamic effects in sedative doses (7), mild respiratory depression (8), relief of anxiety (9), and anterograde amnesia (10). Because of high patient acceptance and a low incidence of adverse effects when used as a sedative-hypnotic (11), midazolam has been suggested for induction of anesthesia as well.

Studies comparing midazolam and diazepam for induction of anesthesia have shown similar spectra of activity, except for greater potency (3), shorter duration of action (6), and lower incidence of venous irritation (3) of midazolam. In contrast to thiopental as an induction agent (12), midazolam tends to produce neither apnea of long duration (13), bronchoconstriction (14), nor laryngospasm (13), but it does cause ventilatory depression of longer duration than thiopental (correlating with its longer-acting sedative effect) (8, 15). The present study was undertaken to compare the hemodynamic effects of induction doses of midazolam and thiopental in healthy surgical patients.

Methods

Twenty A.S.A. class I or II male or nonpregnant female patients, aged 24 to 65 years, scheduled to undergo elective surgical procedures for which arterial and central venous catheters would ordinarily be placed, consented to participate in this study, as approved by the institution's Subcommittee on Human Studies. The mean age of patients in each group was 46; the mean weight of the six male and five female patients receiving midazolam was 65 kg and the mean weight of the six male and three female patients given thiopental was 67 kg. The mean morphine dose in patients given midazolam was 17 mg, whereas the mean morphine dose in those given thiopental was 19 mg. After morphine (0.1 mg/kg IM) premedication and additional morphine (up to 0.2 mg/kg IV) for sedation during arterial and central venous catheter placement, patients were given N_2O-O_2 (4:2 L/min) to inhale by mask. All patients were arousable and at this point breathed spontaneously.

After a stable base line of sedation and cardiovascular stability was achieved, control measurements of mean arterial pressure (MAP), mean right atrial pressure (MRAP), and heart rate (HR) were obtained from the strip recording of a Hewlett-Packard 8-channel monitor (model 7758), using Statham transducers (model P23) and electrocardiogram lead II. Cardiac output (CO) was determined using a Lexington Instruments cardiodensitometer (model R509045) through computerized integration of radial arterial indocyanine green dye concentration following rapid injection of 5 mg of dye into the central venous circulation. Stroke volume (SV) and systemic vascular resistance (SVR) were derived from the measured data.

Following the base line measurements, doses of either midazolam (0.25 mg/kg) or thiopental (4.0 mg/kg) sufficient to induce anesthesia in most premedicated patients, selected randomly, was given intravenously as a bolus injection in double-blind fashion. The doses were equivalent in that midazolam is approximately 15 times as potent as thiopental in inducing anesthesia (13). As patients lost consciousness, ventilation was assisted by mask when needed so as to approximate base line respiratory gas exchange. Additional measurements of MAP, MRAP, HR, and CO were made 2, 5, and 10 minutes after administration of the study drug. No other manipulation of the patient was allowed until the study period had ended, after which tracheal intubation was performed, maintenance anesthetics were added, and surgery began.

Base line control values for each patient were compared with individual measurements at 2, 5, and 10 minutes, using Student's t-test for paired samples. Mean changes in each measurement for all patients given thiopental (N = 9) were then compared with corresponding mean changes for all patients given midazolam (N = 11) using Student's t-test for independent samples. Two-way analysis of variance was used to confirm the reported t statistics and the equivalence of the starting populations for each hemodynamic measure. Differences were considered statistically significant when p was less than 0.05.

Results

The data for the study are summarized in the Table and in the Figure. In patients induced with thiopental, MAP, HR, CO, and SV all decreased below base line values over the 10 minutes of the study. During this time, MRAP increased slightly, whereas SVR did not change. Statistically significant differences from control values included the decline in MAP at 2 and 10 minutes, the increase in MRAP at 10 minutes, and the decrease in CO at 5 minutes.

Changes in patients receiving midazolam were similar to those in patients given thiopental, but the effects were somewhat less pronounced and less rapid in onset. In comparison to control measurements, 2 minutes following midazolam only MAP and SVR declined, whereas MRAP, HR, CO, and SV did not change. At 5 minutes and at 10 minutes, MAP, HR, CO, and SV decreased slightly, but no further changes in MRAP or in SVR were observed. The only statistically significant differences from control were the 5- and 10-minute decreases in MAP.

The two groups were similar with regard to age, weight, morphine premedication, and Pa_{CO_2} levels following assisted ventilation. However, there were no significant differences between the two groups in any measured or derived parameter at any time.

Discussion

As the standard against which all other anesthetic induction agents must be compared, thiopental has been extensively investigated over the past several decades. Cardiovascular effects, in particular, have been examined in isolated myocardial and vascular muscle strips, in laboratory animals, in human volunteers, and in anesthetized surgical patients (16). Although there is a general consensus that thiopental effects a reduction in CO and MAP, authors have disagreed as to whether the primary cause is myocar-

TABLE
Cardiovascular Effects of Midazolam and Thiopental*

	CO	MAP	MRAP	HR	SVR	SV
	L/min	*mm Hg*		*beats/min*	*mm Hg/L/min*	*ml*
Midazolam						
Base line	6.8 ± 2.7	101 ± 18	6 ± 3	85 ± 18	15 ± 5	80 ± 25
2 min	6.8 ± 2.3	89 ± 13	7 ± 3	86 ± 14	13 ± 3	80 ± 24
5 min	6.4 ± 2.3	85 ± 13†	7 ± 3	83 ± 14	13 ± 4	78 ± 26
10 min	6.2 ± 2.0	83 ± 13†	7 ± 3	83 ± 14	13 ± 3	75 ± 22
Thiopental						
Base line	6.9 ± 1.5	95 ± 12	6 ± 4	83 ± 13	13 ± 2	89 ± 29
2 min	6.5 ± 1.6	87 ± 12†	8 ± 5	79 ± 12	13 ± 3	85 ± 27
5 min	6.0 ± 1.3†	87 ± 16	9 ± 5	76 ± 11	13 ± 4	81 ± 23
10 min	6.0 ± 1.3	83 ± 14†	8 ± 4†	78 ± 9	13 ± 3	77 ± 16

* Values are means ± SD.
† $p < 0.05$ as compared with base line.
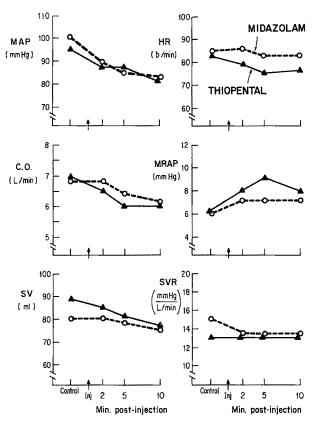
FIGURE. Cardiovascular effects produced by midazolam and thiopental. Significant changes from control levels were noted for mean arterial pressure (MAP) at 5 and 10 minutes following administration of midazolam and for MAP at 2 and 10 minutes, cardiac output (CO) at 5 minutes, and mean right atrial pressure (MRAP) at 10 minutes following administration of thiopental.

dial depression or peripheral arterial or venous dilation. Evidence for the former includes depression of CO by thiopental in the fact of increasing MRAP in the dog heart-lung preparation (17) and its reduction of myocardial contractile force (18). Similar conclu-

sions were reached by Bendixen and Laver (19) studying intact dogs.

Clinical studies supporting the concept of thiopental as a direct myocardial depressant include the work of Elder et al (20) and Flickinger et al (21), whose patients experienced reductions in cardiac index and MAP as well as a slight increase in SVR, which was felt to be compensatory. The concept of thiopental as a peripheral vasodilator is supported by the clinical study of Etsten and Li (22), who concluded that thiopental causes venous pooling which leads to decreased blood return to the right atrium with subsequent decrease in cardiac index, not primarily due to myocardial depression. Fieldman et al (23) also concluded that the observed reduction in central blood volume after thiopental reflected peripheral vasodilation and not direct myocardial depression.

Diazepam, because of its minimal cardiorespiratory effects, even in sick patients, when used in sedative doses (24–26), was proposed in the 1960s as an alternative to thiopental for induction of anesthesia. Rollason (27), for example, found diazepam to induce anesthesia satisfactorily in unpremedicated patients at a mean dose of 0.44 mg/kg (range 0.16 to 0.83 mg/kg) and in premedicated patients at a mean dose of 0.23 mg/kg (range 0.11 to 0.50 mg/kg). Fox et al (28), in comparing thiopental (4.1 mg/kg) with diazepam (0.33 mg/kg), observed a smoother, more gradual induction with diazepam, although decreases in blood pressure and increases in heart rate were similar in the two groups. Dechêne and Desrosiers (29) also compared diazepam and thiopental and found that in premedicated patients a mean dose of 0.46 mg/kg of diazepam caused less respiratory depression, less stimulation of tracheobronchial secretions, less bronchoconstriction, and less hemodynamic change than

thiopental (7.11 mg/kg). Knapp and Dubow (30) reported that no patients given diazepam (0.2 mg/kg) experienced decreases in MAP more than 15% from control levels whereas 67% of patients given thiopental (2 mg/kg) had decreases in blood pressure in excess of 15%. Furthermore, only 1% of patients given diazepam sustained more than a 15% reduction in cardiac output (in contrast to 85% of thiopental patients). On the other hand, Rao and colleagues (31) found that high-dose diazepam (0.77 mg/kg) was associated with myocardial depression (as reflected by decreased blood pressure, SV, CO, and by increased HR and SVR) in healthy patients.

As an intravenous sedative, however, a disadvantage of diazepam is venous irritation during injection and subsequent phlebitis (secondary to its propylene glycol carrier) that it produces. Korttila and Aromaa (32), however, observed a greater incidence of thrombosis and thrombophlebitis after thiopental (2.5% solution) than after diazepam.

The development of midazolam gave rise to the expectation that this newer benzodiazepine might offer the same respiratory and cardiovascular advantages over thiopental as did diazepam, but without the venous irritation or long-acting central nervous system effects associated with diazepam. When Jones et al (33) studied midazolam in dogs, doses as high as 10 mg/kg produced minimal changes in MAP, HR, CO, SV, and SVR. In evaluating midazolam (in a fixed dose of 0.15 mg/kg) as an induction agent in man, Fragen et al (13) found MAP to decrease 25% or more from control values in two of 25 patients and HR to increase 25% or more in four of 25 patients; the hemodynamic effects were not significantly different from those observed in patients in whom anesthesia was induced with thiopental (3.0 mg/kg) or with diazepam (0.3 mg/kg). Reves et al. (34) studied induction of anesthesia with midazolam (in a fixed dose of 0.2 mg/kg) in patients with ischemic heart disease after morphine-scopolamine premedication and noted significant decreases in MAP, SV, and SVR with a significant increase in HR. Cardiac output, as well as MRAP, mean pulmonary arterial pressure, and pulmonary capillary wedge pressure, were, however, not significantly changed. Samuelson and co-workers (35) studied a similar group of patients in whom anesthesia was induced with midazolam (in a fixed dose of 0.2 mg/kg) while breathing 50% N_2O-O_2 instead of 100% O_2. The addition of N_2O appeared to blunt the vasodilatory effects of anesthesia induction. Although a similar array of cardiovascular effects occurred, significant reductions from preinduction levels were

noted only for pulmonary arterial pressure, pulmonary capillary wedge pressure, and SV.

The present study compared midazolam and thiopental under identical preinduction conditions at a predetermined dose schedule in a double-blind fashion. The findings that thiopental (4.0 mg/kg) caused reductions in MAP, CO, HR, and SV; an increase in MRAP; and no change in SVR are consistent with much of the clinical information cited above. Thiopental acts primarily as a myocardial depressant, not as a peripheral vasodilator, at least under the conditions of this study.

Compared with thiopental, midazolam exerts more gradual effects on the circulation in parallel with its more gradual induction of anesthesia. At a 0.25 mg/kg dose of midazolam in healthy patients after morphine sedation and with 66% N_2O inhalation, the only circulatory changes after 2 minutes were decreases in MAP and SVR. At 5 and 10 minutes, CO, HR, SV, as well as MAP decreased slightly, whereas MRAP did not change and SVR showed no further alteration. The only significant changes from base line were the decreases in MAP (16% to 18%) at 5 and 10 minutes. The cardiovascular responses of midazolam induction under these conditions are characterized by central nervous system-induced disruption of heightened sympathetic tone, i.e., the induction of an anesthetic state. Midazolam tends to maintain CO, HR, SV, and MRAP at control levels better than thiopental.

Despite the differences in cardiovascular performance produced by these two drugs, no significant differences in any measured or derived parameter could be determined at any time in this study. Hence, from the cardiovascular point of view, midazolam appears to offer some theoretical advantages over thiopental and, clinically, is at least as good as thiopental as an anesthesia induction agent in healthy patients. The relative value of midazolam compared with thiopental as an induction agent in sicker patients remains to be determined.

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Effects of Dilution, Pressure, and Apparatus on Hemolysis and Flow Rate in Transfusion of Packed Erythrocytes

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CALKINS, J. M., VAUGHAN, R. W., CORK, R. C., BARBERII, J., AND ESKELSON, C.: Effects of dilution, pressure, and apparatus on hemolysis and flow rate in transfusion of packed erythrocytes. Anesth Analg 1982;61:776-80.

The purpose of this prospective, randomized study was to measure both the independent and interactional effects of dilution, pressure, and apparatus on flow rates and hemolysis during rapid administration of erythrocytes. Administration of undiluted erythrocytes increased the concentration of plasma-free hemoglobin by as much as 270% per unit under certain conditions. Transfusion flow rates for packed red blood cells were found to be determined by dilution, pressure, and apparatus and varied by as much as 450%. No significant correlation was found between flow rate and hemolysis. Regardless of the external bag pressure applied or the transfusion apparatus used, packed erythrocytes should be diluted (with at least 100 ml of normal saline) to decrease hemolysis and increase flow rate.

Key Words: TRANSFUSION: hemolysis.

COMPONENT therapy rather than whole blood has become a mainstay of blood transfusion. Hence, anesthesiologists continually face the resultant problem: how should packed erythrocytes (PRBCs) be transfused to minimize hemolysis while maximizing flow rate? Transfusing viable red blood cells will maintain a long-term oxygen-carrying capacity while minimizing the risk of any undesired sequelae produced as a result of an increased circulating concentration of cellular contents and stroma (1).

Presently, no data exist to guide the optimal rapid administration of packed red blood cells (PRBCs). The purpose of this prospective, randomized study was to measure both the independent and interactional effects of dilution, pressure, and apparatus on

red blood cell (RBC) hemolysis and flow rate so as to indicate better methods for transfusion therapy in situations requiring rapid infusion of PRBCs.

Methods

A 3 x 2 x 2 factorial in vitro experimental design was used to assess the effects of dilution, external delivery pressure, and apparatus on both hemolysis and flow rate. Twelve units (bags) of PRBCs were obtained from the hospital blood bank. Three levels of dilution [none, 100 ml of normal saline (NS), and 200 ml of NS], two levels of external bag pressure (150 or 300 torr), and two types of apparatus (abbreviated or complete) were used. Aliquots from the 12 units were allocated by a table of random numbers to each treatment combination.

The complete apparatus (Fig 1) consisted of a recipient set (Travenol Y set) with NS attached to one side and the unit of packed cells to the other. Before attachment, a blood filter (Pall Ultrapore SQ-405) was inserted into the RBC unit. The outlet of the recipient set was connected to a blood warmer (Dupaco Hemocoil) maintained at 37°C. The warming coil was connected to an extension tube (McGaw V5404), a
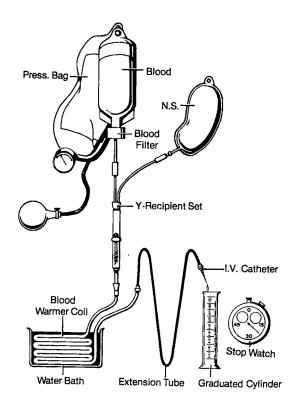
FIG 1. Complete apparatus consisting of Travenol Y-recipient set with normal saline (NS) and packed red blood cells (PRBCs) and Pall Ultrapore filter. Dupaco Hemocoil, a McGaw extension set, a Pharmaseal three-way stopcock, and a Vicra Quick-Cath catheter all connected in series. Abbreviated apparatus consists of only the Y-recipient set and catheter. Fenwal pressure bags supplied external delivery pressure.

three-way stopcock (Pharmaseal K75), and a 16-gauge intravenous catheter (Travenol Quick-Cath). Pressure bags (Fenwal) supplied the external delivery pressure. For the abbreviated apparatus, only the recipient set with appropriate solutions and the intravenous catheter were used.

Before assembly, the composition of each unit of blood was characterized according to age, blood type, and hematocrit level. After the 12 units were assembled, 72 paired aliquots of blood (5 ml each) were randomly sampled (six pairs from each unit). Samples were drawn using a random number table. For each pair, one sample was obtained from the bag by syringe and needle through a sample port placed in the bag before flow. This was considered the inlet sample. The other sample was obtained at the intravenous catheter outlet as blood flowed through the administration apparatus. This was considered the outlet sample. In order to eliminate transients and to reach steady state, blood was allowed to flow for 5 seconds through the apparatus before sampling.

Free hemoglobin was measured in each of the paired samples. Hematocrit level of the sample drawn at the outlet of the apparatus was also measured. Other measurements made in each of the six paired observations were flow volume (measured with a graduated cylinder) and flow time (measured with a stopwatch). Flow rate was calculated by dividing flow volume by flow time. Free hemoglobin was measured by a modification of the spectrophotometric method described by Jacobs and Fernandez (2) and by Van-zetti and Valente (3). These assays are based on the peroxidase activity of hemoglobin using diansidine rather than benzidine as the substrate.

Typical transfusion methodologies were simulated. Packed RBCs, undiluted or diluted with different volumes of NS, were allowed to flow through the administration systems. Collected samples were centrifuged. Supernatant plasma was extracted with Pasteur pipettes for free hemoglobin determination spectrophotometrically using the plasma hemoglobin method described. Hemolysis was measured as a change of free hemoglobin concentration in the plasma between initial and outlet blood samples.

Three-way analysis of variance assessed the main and interactional effects of dilution, pressure, and apparatus on hemolysis (the difference in free hemoglobin concentration, outlet-inlet) and flow rate. One-way analysis of variance and the Student's t-test for grouped data were used for univariate comparisons. Following a significant one-way analysis of variance, Scheffe's method was used to detect differences in means. Linear regression examined the association of extraneous variables with flow rate and hemolysis. Statistical significance was defined as $p < 0.05$.

Results

A description of the 12 units of PRBCs studied is presented and summarized in Table 1. Experimental conditions for each unit are also described.

The degree of dilution was the only independent variable that significantly affected hemolysis as measured by increase in free hemoglobin concentrations (Table 2). However, a three-way interaction effect of dilution, external driving pressure, and apparatus was noted ($p = 0.024$). Undiluted PRBCs resulted in a significantly greater increase in free hemoglobin concentration than did dilution with either 100 or 200 ml of NS ($p < 0.05$) for both a concentration (mg/ml) and total per unit basis (mg/unit) (Table 2). As shown

in Table 2, changes in concentration and total free hemoglobin per unit were greater without dilution for the abbreviated apparatus at 300 torr than at 150 torr. The reverse was found for the complete apparatus with the maximum hemolysis occurring without dilution, complete apparatus, and 150 torr driving pressure (4.71 mg/dl and 2.7 mg/unit, respectively). Values near zero and negative values are not significantly different from zero.

Flow rate (Fig 2) was a significant function of all three independent variables [dilution, external driving pressure, and apparatus ($p < 0.001$)] and also a function of a two-way interaction between dilution and apparatus ($p < 0.001$) (Fig 2). Lowest flows of 6.0 ± 0.2 ml/min were measured for units undiluted, the complete apparatus, and an external pressure of 150 torr. The maximum flow rate (166.8 ± 12.3 ml/min) was measured for units with 200 ml of NS dilution, the abbreviated apparatus, and 300 torr pressure. In general, with the higher pressure, the greater dilution,

and the shorter flow tubing, flow rate increased (Fig 2).

Discussion

Transfusion of PRBCs should be accomplished using methods that facilitate long-term erythrocyte oxygen-carrying capability with minimum risk of undesirable sequelae (1) such as an increase in the circulating concentration of cellular contents (primarily free hemoglobin) and cellular debris (stroma) produced by red cell damage (4). Only solutions containing erythrocytes (PRBCs, whole blood) with adequate intracellular hemoglobin are routinely available and effective in carrying an appropriate amount of oxygen for tissue metabolism over a long-term basis.

Factors affecting the viability of red blood cells can be divided into two groups—biochemical and me-

TABLE 1

Initial Characteristics of Units of Packed Red Blood Cells and Experimental Conditions

Unit	Type*	Age†	Pressure	Apparatus‡	Normal saline dilution	Hematocrit§
		days	torr		ml	
1	O+	24	150	A	0	89.9 ± 0.8
2	A+	24	150	A	100	53.4 ± 2.2
3	O+	19	150	A	200	42.3 ± 1.7
4	AB+	24	300	A	0	83.2 ± 0.3
5	O−	21	300	A	100	56.4 ± 0.7
6	O+	21	300	A	200	43.6 ± 0.9
7	AB+	24	150	C	0	81.2 ± 0.4
8	O+	19	150	C	100	61.1 ± 0.9
9	O+	19	150	C	200	46.1 ± 0.9
10	A+	21	300*	C	0	71.6 ± 0.7
11	O+	24	300	C	100	55.7 ± 1.0
12	A+	24	300	C	200	43.2 ± 0.8

* Type: A (n = 3), AB (n = 2), O (n = 7).
† Age: 19 days (n = 3), 21 days (n = 3), 24 days (n = 6).
‡ Abbreviations used are: A, abbreviated apparatus, C, complete apparatus.
§ Values are means ± SEM.

FIG 2. Effects of dilution, pressure, and apparatus on flow rate. For each dilution, flow rate was significantly increased for abbreviated apparatus at 300 torr ($p < 0.05$).

TABLE 2

Effect of Dilution on Free Hemoglobin (FHb₄) for Given Apparatus and External Pressure*

Normal saline dilution	Change FHb₄ concentration				Change FHb₄ per unit†			
	Abbreviated		Complete		Abbreviated		Complete	
	150 torr	300 torr	150 torr	300 torr	150 torr	300 torr	150 torr	300 torr
ml	mg/dl				mg/unit			
0	−0.55 ± 2.8	2.28 ± 1.75	4.71 ± 2.09	0.55 ± 0.41	−0.11 ± 0.92	0.99 ± 0.88	2.7 ± 1.17	0.47 ± 0.36
100	−0.3 ± 0.10	−0.40 ± 0.22	−0.21 ± 0.51	−0.20 ± 0.09	−0.02 ± 0.18	−0.72 ± 0.38	−0.85 ± 1.12	−0.36 ± 0.15
200	−0.13 ± 0.07	0.37 ± 0.11	−0.10 ± 0.07	−0.09 ± 0.06	−0.39 ± 0.22	1.02 ± 2.7	−0.36 ± 0.24	−0.23 ± 0.16

* Values are means ± SEM; $p < 0.05$ among three dilution groups.
† Calculated assuming total volumes after each dilution of 250, 350, and 450 ml, respectively.

chanical (1). Biochemical factors that characterize PRBC (age, blood type) cannot be directly controlled by the anesthesiologist. However, mechanical variables affect the destruction of erythrocytes during transfusion and can be influenced by the anesthesiologist. These variables can be classified as intracellular and extracellular (1). The primary intracellular variable affecting cellular integrity is osmotic pressure resulting from the amount and type of solution used for RBC suspension. Extracellular variables result from the forces existing within the flowing solution and can be described using rheologic principles (5).

Investigations of cellular destruction in blood flow systems have noted that the magnitude of hemolysis is directly proportional to magnitude of shear stress (6) and cellular-solid surface interactions (7). Shear stress is the resultant force acting on cells. That stress is directly proportional to the degree of aggregation or amount of force required to start flow (yield stress), the resistance of the fluid to flow (viscosity), and velocity changes across the flow channel (rate of shear) (5). Yield stress and viscosity are affected directly by hematocrit and plasma protein concentration. Rate of shear is a direct function of the type of fluid and flow (laminar or turbulent). Shear stress, hence hemolysis, is a direct function of hematocrit, protein concentration, and the type of flow. As each of these variables is also a direct function of dilution, more dilution produces less hemolysis (Table 2).

Whether hemolysis can be completely attributed to shear stress is uncertain. Eurenius and Smith (8) have demonstrated increased hemolysis from increased infusion pressure and erythrocyte age. In addition to the effects of age and infusion pressure, Leverett et al (7) suggested that at a threshold shear stress level greater than 1500 dynes/cm,^{2} extensive cell damage results directly from shear stress with minimal effects from the secondary factors of solid surface interaction. In this experiment, shear stress was estimated (shear stress = pressure × radius/2 × length) to vary from 150 to 600 dynes/cm^2. This implies that secondary factors play an increased role in cellular destruction.

The increased hemolysis that appeared in the present experiments with the complete apparatus at the lower pressure (150 vs 300 torr) without dilution (Table 2) could result from the confounding variables of hematocrit (81.2 vs 71.6), and age (24 vs 21 days) as suggested by Eurenius and Smith (8), as well as possible increased interactions between the RBCs and the tubing surface as suggested by Leverett et al. (7).

Flow rate is a direct function of the type of flow.

For Reynolds numbers [Reynolds number = (density × velocity × diameter)/viscosity] of less than 2100, laminar flow exists. For the conditions investigated, all Reynolds numbers were less than 900. Because laminar flow existed, trends in flow rate can be estimated as a direct function of yield stress, pressure, and the fourth power of the radius and an inverse function of viscosity and tubing length (5, 8). Therefore, increased hematocrits (increased viscosity), longer lengths of tubing (complete apparatus), and no external pressure (decreased driving force) will result in diminished flow rates as presented in Fig 2.

Lack of correlation between flow rate and change in free hemoglobin concentration may have resulted because laminar flow existed throughout the experimental conditions. At Reynolds numbers greater than 2100 (turbulent flow and increased shear stress), the change in free hemoglobin concentration may be a function of flow rate.

The present experiment was designed for situations requiring the rapid infusion of PRBCs. However, some indication of the magnitudes of flow rates and hemolysis for situations in which no pressure bags were used (i.e., gravity flow) might be inferred from the results. From the data and previous discussion, the maximum flow rate (166.8 ± 12.3 ml/min) would be reduced to approximately 50 ml/min for gravity flow if the height between the blood unit and transfusion outlet were 4 ft without a pressure bag. This predicted value results from the direct relation between pressure and flow (flow B = flow A × pressure B/pressure A). Hemolysis should be less than that obtained (Table 2). In an in vitro pilot study that utilized a similar methodology with 18-day-old whole blood (hematocrit 35), results of this magnitude were obtained for gravity flow. For analogous conditions of gravity flow with both the abbreviated and complete apparatus, flow rates of 52.6 ± 1.9 ml/min and 13.3 ± 0.05 ml/min were obtained. The measured free hemoglobin was 0.44 and 0.17 mg/dl, respectively.

In conclusion, regardless of the external bag pressure applied or the transfusion apparatus used, PRBCs should be diluted to decrease hemolysis and increase flow rate. Although PRBC flow rate is determined by dilution, pressure, and apparatus, no significant correlation was found between flow rate and hemolysis. Administration of undiluted PRBCs increases mechanical damage to the RBCs by known rheologic factors (shear stress) and cellular material interactions resulting in an increase in free hemoglobin concentration.

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Esophageal Lead for Intraoperative Electrocardiographic Monitoring

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The use and safety of the esophageal electrocardiogram for detection and diagnosis of dysrhythmias or ischemia during anesthesia was compared with the conventional electrocardiogram using leads II and V₅ in 20 patients undergoing coronary artery bypass graft surgery. Using an intra-atrial electrocardiogram as the standard to provide detection and definitive diagnosis of dysrhythmias, the correct diagnosis from leads II and V₅ was made in 53.8% and 42.3% of cases, respectively, whereas 100% of the dysrhythmias were properly diagnosed from the esophageal electrocardiogram ($p < 0.05$). In two patients, the presence of a significant dysrhythmia was not detected using standard leads II and V₅ alone. Large, distinct P waves, resulting from the proximity of the esophageal lead to the left atrium, clearly established the temporal relationship between atrial and ventricular depolarization. Posterior myocardial ischemia was diagnosed in one patient by ST-segment elevation in the esophageal electrocardiogram, whereas leads II and V₅ did not demonstrate ischemic changes. No complications were encountered during the study. The esophageal lead is safe, simple to use, and provides valuable information for detection or diagnosis of dysrhythmias and myocardial ischemia during anesthesia.

Key Words: MONITORING: electrocardiography, esophageal; HEART: esophageal electrocardiography.

COMPLEX dysrhythmias occasionally occur during anesthesia and often pose difficult diagnostic problems. As major hemodynamic consequences can result from these dysrhythmias, rapid and accurate detection and diagnosis are important. The clear identification of atrial activity from distinct P waves is often necessary for differentiation of various types of dysrhythmias (1). Standard electrocardiogram (ECG) lead II is frequently observed for this purpose (2). Unfortunately, however, even the conventional 12-lead ECG may not provide distinct P waves, especially in the presence of tachycardias (1, 3). Placement of an ECG electrode near atrial tissue, such as in the esophagus just posterior to the atrium or in the atrium itself, results in augmented P waves on the ECG and clearly establishes the relationship of atrial to ventricular activity (4).

Intra-atrial electrograms (AEG) have been used in cardiac electrophysiologic laboratories to evaluate the temporal sequence of cardiac depolarization (5). This technique precisely confirms mechanisms of complex cardiac rhythms, resulting in a rapid, definitive diagnosis of most dysrhythmias (5). For many years, the esophageal electrocardiogram has also been known to be a valuable technique for evaluation of dysrhythmias in nonsurgical patients (6, 7). P waves that were absent or barely discernible on the standard 12-lead ECG have been shown to be prominent and distinct on an esophageal ECG (6). Compared with lead II, the esophageal lead has been found to be superior for elucidating the exact nature of complex dysrhythmias (8).

The esophageal ECG has also been shown to be useful for evaluating ischemia of the left ventricle (9). The diagnosis of posterior ischemia and infarction, often difficult using conventional ECG leads, is facilitated by the esophageal ECG due to its proximity to the posterior aspect of the left ventricle (10, 11).

Considering the limitations of the surface ECG, this investigation was designed to evaluate the use and safety of the esophageal ECG for detection and diagnosis of dysrhythmias during anesthesia by comparing it with the standard ECG and the AEG. In addition,

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changes in ST segments reflecting posterior myocardial ischemia were assessed.

Methods

After approval by the Human Investigations Committee, 13 men and seven women, aged 49 to 69 years, scheduled for elective coronary artery bypass grafting, gave informed consent and were included in the study. All patients had normal sinus rhythms; however, five patients had evidence of conduction problems, two with first degree heart block, and one each with right bundle branch block, left bundle branch block, and left anterior hemiblock. One patient also had chronic premature ventricular contractions. Sixteen patients received beta-adrenergic receptor blocking drugs until the morning of surgery, and three others were chronically receiving digoxin.

Conventional intraoperative electrocardiographic analysis consisted of a 7-lead ECG (I, II, III, aVR, aVL, aVF, V$_5$) monitored with a Hewlett-Packard 78208A ECG monitor with a lead selector and recorded on a Gould 2800 7-channel recording system. Each patient had an Edwards multipurpose Swan-Ganz catheter inserted before anesthetic induction via the right internal jugular vein using the Seldinger technique. This pulmonary arterial catheter is equipped with two intraventricular pacing electrodes located 18.5 and 19.5 cm from its distal end, and three intra-atrial electrodes situated 28.5, 31.0, and 33.5 cm from the distal end. Correct position of the intra-atrial electrodes was verified by their atrial pacing capability at a threshold less than 20 mamp using a Medtronic #5337 external pacemaker. Two of the intra-atrial electrode wires were then incorporated as the right arm and left arm electrodes in a lead I ECG circuit and monitored as a bipolar AEG. This intracardiac electrogram was used as the standard from which definitive dysrhythmia diagnoses were made.

The esophageal ECG was a #24 French esophageal stethoscope modified with two external chloridized silver wire electrodes 0.95 cm in width and situated 7 and 20 cm from the distal end of the stethoscope (Fig 1). Each electrode wire was extruded through the wall of the stethoscope to its proximal end and chemically welded to a standard ECG lead wire. A Hewlett-Packard #14392A electrocautery protection filter consisting of a 3 mHz inductor and a 10 k-ohm resistor was inserted into the esophageal ECG circuit between the esophageal ECG lead wires and the monitor cable. Incorporation of the esophageal leads as the right arm and left arm electrodes of lead I established a bipolar
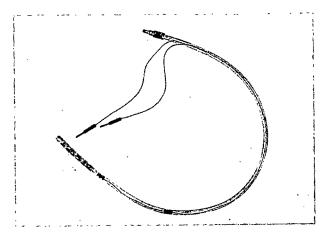
FIG 1. Modified esophageal stethoscope showing two external coil electrodes and ECG lead wires.

esophageal ECG circuit. The esophageal stethoscope was inserted blindly via the mouth after tracheal intubation and it was positioned at the point of the maximum positive P wave amplitude appearing on the ECG monitor, distal to the point at which a biphasic P wave was observed. This resulted in the electrodes being positioned posterior to the left ventricle, just inferior to the atrioventricular groove. The position of the stethoscope was not changed after the patients were given anticoagulants. All of the ECG monitors were electrically isolated and recorded at a paper speed of 25 mm/sec with a standardization of 1 mV = 10 mm.

ECG leads II and V$_5$, as well as the esophageal ECG, were continuously monitored and observed for dysrhythmias. If a dysrhythmia was suspected in any of these leads, the AEG was recorded and a definite diagnosis was obtained. The diagnosis of dysrhythmias was made in order from recordings of leads V$_5$ and II, esophageal ECG, and then the AEG. The diagnosis from the esophageal ECG and surface ECG were considered correct if they were the same as the diagnosis obtained from the AEG. The dysrhythmias were analyzed as to type, frequency, time of the surgery during which they occurred, and incidence of misdiagnosis by either standard or esophageal leads. Myocardial ischemia was diagnosed by ST segment depression or elevation > 1 mm in the standard or esophageal ECG. All patients were questioned after surgery for symptoms of esophageal discomfort.

The incidence of misdiagnosis using leads II, V$_5$, and the esophageal ECG was compared using chi-square two-variable tests. Statistical significance was determined at the $p < 0.05$ level.

TABLE

Comparison of Esophageal Electrocardiogram (ECG) and Standard ECG for Correct Dysrhythmia Diagnosis

Dysrhythmia	No.	Correct diagnosis		
		V_5	II	Esophageal
Sinus bradycardia	4	4	4	4
Sinus tachycardia	1	1	1	1
1° heart block	1	0	0	1
2° heart block	2	0	0	2
3° heart block	4	0	1	4
Frequent premature ventricular contractions	2	2	2	2
Frequent premature atrial contractions	5	2	3	5
Atrial flutter	2	0	0	2
Atrial fibrillation	3	2	2	3
Paroxysmal atrial tachycardia	1	0	0	1
Nodal rhythm	1	0	0	1
% correct	—	42.3	53.8	100
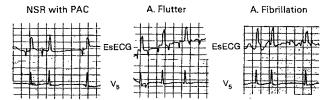
FIG 2. Dysrhythmia progression in one patient is shown. Esophageal ECG (EsECG) distinctly reflects changes in atrial rhythm from normal sinus rhythm (NSR) with one premature atrial contraction (PAC), to atrial flutter (A. Flutter), and atrial fibrillation (A. Fibrillation). Lack of information about atrial activity from lead V_5 made definitive diagnosis impossible.

Results

Twenty-six episodes of sustained dysrhythmias occurred in 14 patients and six patients had no dysrhythmias (Table). Twenty percent of the dysrhythmias occurred before opening or after closing the chest and included atrial flutter, sinus bradycardia, sinus tachycardia, and premature ventricular contractions, all of which required treatment. The 62% of dysrhythmias that occurred immediately before cardiopulmonary bypass usually developed during atrial cannulation. The most common dysrhythmias with the chest open were premature atrial contractions, atrial flutter, or atrial fibrillation associated with atrial cannulation, and second and third degree heart block associated with return of cardiac rhythm after hypothermic hyperkalemic cardioplegia.

Using the AEG as the standard, the correct diagnosis was made from leads II and V_5 in 53.8% and 42.3% of cases, respectively (no significant difference), whereas 100% of the dysrhythmias were properly diagnosed from the esophageal ECG lead ($p < 0.05$)

(Table). With both the esophageal ECG and the AEG, the P waves were equally distinct and the temporal relationships between atrial and ventricular depolarizations were clear. Indistinct P waves on standard lead II and precordial lead V_5 resulted in incorrect diagnoses of dysrhythmias, and in two patients, dysrhythmias were missed (Figs 2 and 3).

Figs. 2 to 4 are examples of simultaneous ECGs which demonstrate the advantage of the esophageal ECG over the conventional ECG for identification of atrial activity (Fig 2). During episodes of supraventricular tachycardia or heart block, P waves were
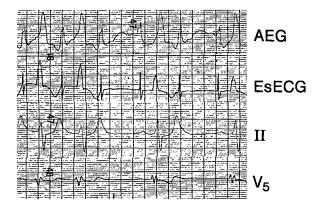
FIG 3. Clear identification of P waves in esophageal ECG (EsECG) and intra-atrial electrogram (AEG) allows for correct diagnosis of first degree heart block and left bundle branch block progressing to second degree heart block, Mobitz type II. P waves are practically lost in down slope of preceding T waves in leads II and V_5 which resulted in incorrect diagnosis of sinus bradycardia rather than second degree heart block.
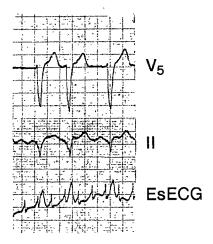
FIG 4. Leads II and V_5 show rhythm strips with a variable heart rate and no discernible P waves; diagnosed as atrial fibrillation. Simultaneous esophageal ECG (EsECG) shows regular P waves at a rate of 280 · min^{-1} with varying atrioventricular block, allowing for correct diagnosis of atrial flutter with varying block.

Baseline

Posterior Ischemia on Bypass
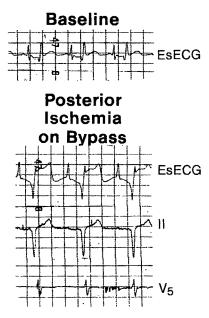
FIG 5. True posterior ischemia with ST segment elevation isolated to esophageal ECG (EsECG). Also, note ease with which diagnosis of a regular sinus rhythm is made from EsECG compared with leads II and V_5.

sometimes lost in the preceding T waves on the surface ECG (Fig 3). Furthermore, the inability of the surface ECG to detect atrial flutter waves clearly resulted in one case of atrial flutter with varying block being diagnosed as atrial fibrillation (Fig 4), and another case of atrial flutter with 2:1 block being diagnosed as normal sinus rhythm from leads II and V_5 (Fig 2, middle panel).

One patient developed ST segment elevation only on the esophageal ECG, not in leads II or V_5 (Fig 5). The ST segment elevation occurred before completion of the proximal anastomosis of a right coronary artery vein graft and resolved shortly after reestablishing blood flow through the graft. This episode represented posterior ischemia which was not detected by the surface ECG leads II or V_5.

The modified esophageal stethoscope allowed clear auscultation of heart and lung sounds in all patients when positioned as described. The endocardial pacing capabilites of the multipurpose Swan-Ganz catheter provided protection during placement of the pulmonary arterial catheter in the one patient with a left bundle branch block. Complications associated with use of the AEG or esophageal ECG were not encountered. Esophageal mechanical trauma was not evident, nor were there any postoperative symptoms suggestive of esophageal injury.

Discussion

Ventricular depolarization is usually easily recognized from a surface ECG. Atrial activity, however, can be indistinct even when observing ECG lead II (8). As inadequate monitoring of the temporal relationships of atrial and ventricular activities can lead to incorrect diagnosis and therapy, it is important to have an ECG that amplifies atrial depolarization and allows the correct rhythm diagnosis to be made. Variations of surface ECG lead placement, such as with the MCL_1 and CB_5 leads, have been used to provide large P wave deflections (12, 13). However, the amplitude of P waves in the MCL_1 and CB_5 leads does not approach that produced by the proximity lead of the esophageal ECG. This study demonstrates not only that the esophageal ECG is easily used in the anesthetized patient, but that it also depicts atrial depolarization as clearly as the AEG. The esophageal ECG was easily inserted, simple to operate, and caused no complications in this series of patients.

The esophageal ECG can be monitored as a bipolar or unipolar ECG circuit. Most investigators have found the bipolar esophageal ECG to be superior, as the P waves are most distinct and less likely to be disguised by a superimposed QRS complex (6). In preliminary trials with these two methods of esophageal ECG circuitry, we noticed less base line fluctuation with the bipolar esophageal ECG in the anesthetized, mechanically ventilated patient. Therefore, this study was performed using a bipolar circuit.

When the esophageal ECG is monitored concurrently with use of the surgical electrocautery, electrical safety precautions should be instituted to minimize the risk of esophageal injury. A ground pad with a large surface area should be properly positioned, and strict electrical isolation of monitoring equipment must be maintained to ensure minimal esophageal electrode current, even if an electrical short circuit were to accidently place a high voltage source between the patient and the recording apparatus (14). All ECG equipment produced after 1972 should meet the American Heart Association recommendations of being incapable of delivering more than 10 μamp of leakage current to a patient (15). In this study, an electrocautery protection filter was incorporated into the esophageal ECG circuit to reduce further the risk of esophageal burn injury. By filtering out radio frequencies above 20 kHz, the protection filter shielded out typical electrocautery currents, but allowed ECG signals to be conducted. The patients in this study had no symptoms of esophageal discomfort in the

early postoperative period after beginning oral intake, suggesting that clinically important esophageal trauma was not encountered.

The esophageal lead has been reported to be the most important lead for detecting posterior myocardial ischemia or infarction (10). The esophageal ECG reflects the electrical potentials of the posterior surface of the heart and responds to posterior ischemia with characteristic ST segment changes (16). The clinical situation and associated esophageal ECG changes shown in Fig 5 are compatible with posterior myocardial ischemia. As this area of the ventricle is adjacent to the esophagus but not the diaphragm, the esophageal ECG demonstrated significant ST segment elevation whereas ECG lead II remained unchanged.

Although this study demonstrated the value of an esophageal ECG during cardiac surgery, this technology could easily be applied to surgical patients during noncardiac surgery and in the early postoperative period in either an intensive care unit or recovery room. The system is relatively noninvasive, and, if sound electrical precautions are observed, should pose no undue risk to the patient.

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technical
COMMUNICATION

Limitations of the Sodium Fusion Assay for Fluorinated Metabolites

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A method involving sodium fusion and analysis by fluoride electrode, which has been used for the determination of total fluorinated metabolites of fluorine-containing drugs in physiologic fluids, is shown to be inapplicable to volatile fluorinated metabolites of volatile fluorinated anesthetic agents. The yields of inorganic fluoride from the volatile metabolites 2,2,2-trifluoroethanol and trifluoroacetaldehyde were less than 2% of expected values, whether these metabolites were present in water, buffer, urine, or hepatic microsomes, although reliable results were obtained for the relatively nonvolatile sodium trifluoroacetate. It is proposed that the assay does not provide a valid method for determining total fluorinated metabolites of volatile or nonvolatile fluorine-containing drugs, but may be of some use in determining a single nonvolatile fluorinated metabolite of a volatile fluorinated drug.

Soltis and Gandolfi (1) have reported a method involving sodium fusion and analysis by fluoride electrode which is proposed to be a general method for the determination of total fluorinated metabolites of fluorine-containing drugs in physiologic fluids. The method is proposed to be applicable to the determination of total fluorinated metabolites in the presence of the parent fluorinated drugs regardless of the volatility or nonvolatility of the parent drug or of its metabolites. We report here on limitations to this assay, namely its inability to determine volatile fluorinated metabolites, and its inapplicability to studies of the metabolism of nonvolatile fluorinated drugs.

Methods and Materials

Materials were obtained as follows: Fluoroxene (Ohio Medical Products, Madison, WI), halothane (Halocarbon Laboratories, Hackensack, NJ), 2,2,2-trifluoroethanol, trifluoroacetaldehyde, and trifluoroacetic acid (Merck Chemicals, Darmstadt, Germany). Isoflurane was a gift from Dr. Julian Biebuyck of Bell Laboratories. Male Long Evans rats (190 ± 10 g) were treated with phenobarbital as described elsewhere (2). Hepatic microsomes were isolated from fresh rat liver by the method of Holtzmann and Carr (3) and were suspended at a concentration of 2 mg of protein per milliliter in 0.02 M Tris-HCl, pH 7.4. Sodium fusion and fluoride analysis were carried out as described by Soltis and Gandolfi (1).

Results and Discussion

The yields of three fluorinated metabolites taken through the sodium fusion assay of Soltis and Gandolfi in various solutions and physiologic fluids are shown in the Table. As can be seen, the yield of sodium trifluoroacetate was approximately 80% to 100% independent of the medium. The yield was decreased to approximately 20% in the case of the free trifluoroacetic acid, presumably as a consequence of incomplete ionization of the volatile acid to the nonvolatile anionic form by the sodium hydroxide added before lyophilization. The yields of the other

TABLE

Sodium Fusion Assay of Fluorinated Metabolites

Metabolite*	Medium	Recovery of fluoride	
		μM	%
2,2,2-Trifluoroethanol	Water	<1	<2
	Tris-HCl†	<1	<2
	Microsomes‡	<1	<2
	Urine	<1	<2
Trifluoroacetaldehyde	Water	1	2
	Tris-HCl	<1	<2
	Microsomes	<1	<2
	Urine	<1	<2
Trifluoroacetic acid	Water	31 ± 2	26
	Tris-HCl	22 ± 2	19
	Microsomes	25 ± 8	20
	Urine	22 ± 5	19
Trifluoroacetate, sodium	Water	100 ± 20	83
	Tris-HCl	120 ± 6	100
	Microsomes	96 ± 15	80
	Urine	100 ± 5	83
	Phosphate§	100 ± 5	83

* To give a final concentration of 120 μM fluoride ion in assay medium.

† 0.02 M, pH 7.4.

‡ At a concentration of 2 mg of protein per milliliter of 0.02 M Tris-HCl, pH 7.4.

§ 0.05 M, pH 7.4.

fluorinated metabolites investigated, such as 2,2,2-trifluoroethanol and trifluoroacetaldehyde, were 2% or less in water, buffer, or physiologic fluids, indicating that the assay is inapplicable to volatile metabolites. As the yields of the parent anesthetic agents (e.g., halothane [20 mM], isoflurane [15 mM], and fluroxene [15 mM] in water and hepatic microsomes) in the assay were less than 0.01% (less than 1 μM fluoride)), metabolites such as 2-chloro-1,1,1-trifluoroethane and 2-chloro-1,1-difluoroethylene (4), which are more volatile than the parent anesthetic agent halothane, would clearly be lost under the conditions of the assay. As many of the metabolites of volatile anesthetic agents such as halothane, fluroxene, and 2,2,2-trifluoroethyl ethyl ether in vitro and/or in vivo are volatile (e.g., 2,2,2-trifluoroethanol, trifluoroacetaldehyde, 2-chloro-1,1,1-trifluoroethane, and 2-chloro-1,1-difluoroethylene) (see e.g., [4–6]), this technique would not provide a valid method for the determination of total fluorinated metabolites of vol-

atile anesthetic agents. In general, the assay could not attempt to provide a measure of the total fluorinated metabolites of volatile fluorinated drugs unless all metabolites were shown to be nonvolatile.

The conversion of a nonvolatile fluorinated drug to total fluorinated metabolites could not be determined by the assay of Soltis and Gandolfi, as the conversion of a nonvolatile drug to nonvolatile fluorinated metabolites would not be accompanied by a net change in the concentration of free fluoride ion. For example, the metabolism of the anorexogenic drug fenfluramine to a nitrone derivative or to norfenfluramine in vitro or in vivo (see e.g., [7, 8]) would result in no net change in fluoride content as assayed by the method of Soltis and Gandolfi (1).

In conclusion, the method of Soltis and Gandolfi (1) does not appear to be suitable for determining total fluorinated metabolites of volatile or nonvolatile fluorinated drugs. The assay might, however, be of use in monitoring the conversion of a volatile fluorinated drug to a single nonvolatile fluorinated metabolite, but only if the structure of the product and its efficiency recovery in the assay were known.

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CLINICAL reports

Anesthetic Management and Monitoring of a Parturient with Mitral and Aortic Valvular Disease

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Approximately 90% of all parturients with rheumatic heart disease have mitral stenosis as the predominant lesion (1). For unknown reasons, mitral regurgitation of rheumatic origin is primarily found in men, so that experience with management of patients with mitral regurgitation during labor and delivery is limited. During labor, systemic resistance is increased by pain, expulsive efforts (Valsalva maneuver), and aortic compression by the uterus. As increases in systemic resistance are poorly tolerated by parturients with regurgitant valvular lesions, control of systemic vascular resistance is a major goal in the management of their labor. In this paper we report the use of lumbar epidural analgesia in a patient with mitral and aortic regurgitation, and the beneficial effects of this technique on the hemodynamic responses that we measured.

Case Report

A 23-year-old gravida 2 para 1 was admitted at 37 weeks of gestation, because of increasing shortness of breath. She had received no prenatal care during this pregnancy. She had a history of acute rheumatic fever, with the first episode

at age 11, one recurrence at age 13, and two recurrences at age 21 years. She had an uncomplicated vaginal delivery of a term pregnancy at age 19 years by natural childbirth. During the current pregnancy she was asymptomatic until the 4th month when she noticed increased fatigue and shortness of breath which resolved after 3 weeks. She had been taking digoxin, 0.25 mg/day, for the past 2 years.

At the time of admission she complained of dyspnea on mild exertion and four-pillow orthopnea. Physical examination revealed an obese white woman (105 kg) with a regular heart beat at a rate of 100 beats per minute. A grade III/VI holosystolic murmur was heard at the apex with radiation to the left axilla. A II/VI diastolic murmur was heard at the left sternal border. Fine basilar rales were heard in both lung fields. Chest roentgenogram showed cardiomegaly and a right middle lobe infiltrate. There were no radiographic signs of pulmonary edema. Her electrocardiogram showed left ventricular hypertrophy and left atrial enlargement.

A diagnosis of probable atypical pneumonia with possible congestive heart failure was made and erythromycin, 250 mg four times a day, and furosemide, 40 mg/day, were started. Over the next 2 weeks her chest roentgenogram cleared and she became asymptomatic. A two-dimensional echocardiogram showed a deformed mitral valve with moderate increase in left atrial size and a marked increase in left ventricular size. In addition, diastolic vibration of the anterior leaflet of the aortic valve was seen, which was consistent with aortic regurgitation.

Because she was close to term, she remained in the hospital and plans were made for management of her labor and delivery. Considering her symptoms of cardiac decompensation in the 4th and 9th months of her pregnancy and the severity of mitral valve deformity on echocardiogram with a concurrent aortic valve lesion, we decided that invasive monitoring would facilitate management of the peripartum period.

It was the consensus of the obstetric service that she be allowed to go into labor spontaneously and deliver vaginally. To achieve the beneficial effects of sympathetic blockade and reduction of systemic resistance so as to augment cardiac output, we planned to use continuous lumbar epidural analgesia during labor.

The patient spontaneously commenced labor 18 days after admission. In the delivery room a Swan-Ganz ther-

modilution pulmonary arterial catheter (Edwards Laboratories) was placed percutaneously through the median basilic vein of the right arm and was advanced into the pulmonary artery. A left radial arterial pressure catheter was also placed. Uterine displacement or the lateral position were maintained during the course of labor. The initial pulmonary arterial (PA) pressure was 41/27 torr, with a pulmonary capillary wedge pressure (PCWP) of 27 torr, and a central venous pressure (CVP) of 10 torr. Systemic arterial pressure was 170/60 torr between contractions. During contractions, pulmonary and systemic pressures increased to 65/40 and 200/60 torr, respectively. Cardiac output measured between contractions by thermodilution was 8.17 L/min (cardiac index = 4.0 L/min/m^2). Calculated systemic vascular resistance (SVR) was 792 dyne$\cdot$sec$\cdot$cm^{-5}, corresponding to an SVR index of 1608 dyne$\cdot$sec$\cdot$m$^2 \cdot$cm^{-5} (normal value = 2000 $\pm$ 300). The changes in measured and

derived cardiovascular parameters during the course of labor and delivery are shown in Fig 1.

An epidural catheter was placed for analgesia and an initial dose of 9 ml of 0.25% bupivacaine was injected. Pulmonary arterial pressure subsequently declined to 35/21 torr, systemic pressure decreased to 154/50 torr, and PCWP declined to 18 to 22 torr. During contractions, increases in PA pressure to 55/30 and systemic pressure to 185/60 persisted after adequate analgesia was obtained. Her arterial blood had pH of 7.46, P_{CO_2} of 27 torr, and P_{O_2} of 119 torr while breathing room air. During the second stage of labor, the patient was instructed to begin bearing down. As shown in Fig 1, her systemic pressure, PA pressure, and PCWP markedly increased during and between her expulsive efforts. The patient delivered a 3000-g male infant with Apgar scors of 4 at 1 minute and 7 at 5 minutes. Immediately after delivery, she developed a persistent cough and on physical
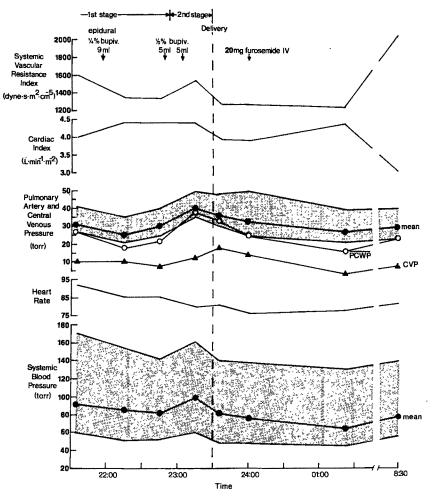
Fig 1. Changes in directly measured and derived indices of cardiovascular function during course of labor and delivery. For pulmonary and systemic arterial pulse pressures, upper border of shaded area represents systolic pressure and lower border represents diastolic pressure. Mean central venous pressure (CVP, ▲), pulmonary capillary wedge pressure (PCWP, O), and mean arterial pressures (●) are denoted. All points represent values measured between contractions at time indicated.

examination was found to have bilateral fine rales and wheezes; PCWP was 34 torr. Arterial blood gas measurements at this time were pH 7.43, P_{CO_2} 33 torr, P_{O_2} 80 torr while breathing room air. Furosemide (20 mg) was administered intravenously 30 minutes after delivery. Cardiac performance improved with decline of PCWP to 16 and PA pressures of 39/21 torr 110 minutes after delivery, with the CVP measuring 3 torr. Nine hours after delivery, and without further diuretic therapy, PCWP and CVP measured 24 and 8 torr, respectively, and physical examination revealed no rales or wheezes. The pulmonary and radial arterial catheters were removed at that time, and the remainder of her postpartum course was uneventful.

Discussion

This case illustrates the value of invasive cardiovascular monitoring in the parturient with valvular heart disease who is undergoing the physiologic changes that accompany labor, epidural analgesia, and delivery. The initial PCWP of 27 torr measured in this patient, while markedly elevated, was consistent with left ventricular dysfunction secondary to the mitral and aortic valvular lesions. The CVP of 10 torr (13.7 cm H_2O) was not increased initially, illustrating the marked disparity that may exist in preload between the right and left sides of the heart. The initial cardiac output of 8.17 L/min was greater than normal, as noted previously in parturients in the first stage of labor (2). In spite of a moderate elevation of systolic blood pressure, the SVR in this patient was initially less than normal at 792 dyne·sec·cm^{-5}, a compensatory decline previously noted in patients with aortic regurgitation (3). The patient's gravid condition may or may not have contributed to a decreased SVR. Although SRV is less than normal from 16 to 36 weeks of gestation, there is a return to near normal values at term (4, 5). However, supine parturient patients, experiencing some degree of aortocaval compression, increase SVR in order to maintain systolic blood pressure (6). Changing to the lateral position with subsequent improvement in venous return leads to an increase in cardiac output and a decrease in SVR (6). Blood squeezed from the contracting uterus increases blood volume (7) and contributes to the increased systemic and pulmonary arterial pressures seen with contractions.

Epidural analgesia resulted in a decrease in SVR index and PCWP, with an increase in cardiac index and left ventricular stroke work; consequently, a dramatic improvement was seen in left ventricular performance. These changes may result from two effects: (a) the segmental sympatholytic effect of the epidural itself, and (b) decreased sympathetic tone associated

with decreased pain of labor. PA and systemic arterial pressures increased almost to preanesthetic levels with contractions, in spite of excellent analgesia. This suggests that blood expressed from the utrine vascular bed during contractions continued to increase blood volume significantly. The increase in uterine vascular resistance accompanying contractions increases the SVR and thus could also contribute to increased systemic and pulmonary vascular pressures. Clinical considerations limited our investigation of cardiovascular changes from rest to contractions. Cardiac output, however, was not altered during contractions, compared with values between contractions.

During the second stage of labor, the parturient's bearing down efforts resulted in a dramatic decline in cardiac performance. This decline was associated with an increase in SVR nearly to values found before epidural anesthesia, in spite of supplemental epidural doses of local anesthetic. The Valsalva maneuver necessary for expulsive efforts involves prolonged increases in intrathoracic pressure with compression of the chambers of the heart and reduction of transmural pressure; this in turn limits cardiac filling with a consequent decrease in stroke volume and cardiac output (8). A compensatory increase in heart rate and increase in SVR occurs which supports systemic blood pressure. With the release of expiratory pressure, the increased SVR results in an elevated blood pressure, which continues for up to 2 minutes. In a patient with frequent contractions, SVR will not return to normal levels before repeated Valsalva maneuvers are required for following contractions. In a patient with aortic and mitral insufficiency, increased SVR results in increased regurgitant flow. In fact, during the second stage of labor, "V-waves" typical of regurgitant flow through the mitral valve transmitted into the pulmonary veins, were present in the PCWP tracing, elevating it above the PA diastolic pressure (Fig 1). Such bearing down efforts were ultimately responsible for the pulmonary congestion that became evident after delivery. Following delivery, the PCWP began to decline from 38 to 25 torr, whereas the CVP increased from 12 to 18 torr immediately postpartum, declining to 14 torr 30 minutes after delivery. The increase in CVP reflects, in part, the increased blood volume due to the blood expelled from the contracted postpartum uterus. The opposed changes in CVP and PCWP emphasize the value of measuring the left ventricular preload (PCWP). Following delivery, there is usually a significant increase in cardiac output (2); however, there was a decline in this patient. This may reflect impaired cardiac performance following the
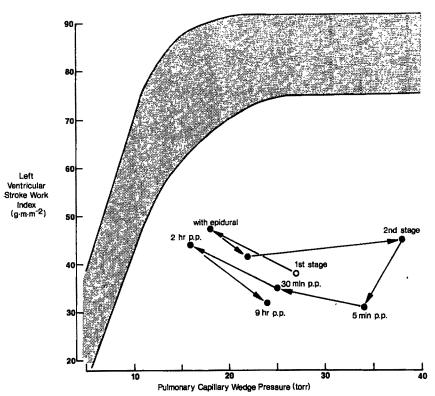
FIG 2. Left ventricular function during course of labor. Calculated value of left ventricular stroke work index (LVSWI) is plotted as function of pulmonary capillary wedge pressure (PCWP) for this patient. LVSWI in grams per meter per meter squared was calculated as: LVSWI = 0.0136 × [cardiac index · (mean systemic arterial pressure − PCWP)]/heart rate. Stippled area shows range of values obtained in patients with normal left ventricular performance.

expulsive efforts of the second stage of labor. Thirty minutes following delivery, PCWP declined to 25 torr while cardiac index remained stable at 3.9 L/min/m^2.

In Fig 2 is provided a measure of left ventricular function by plotting the left ventricular stroke work index (LVSWI in g · m · m^{-2}) as a function of PCWP, as described initially by Sarnoff and Mitchell (9). The shaded region delineates the normal range observed in healthy patients, the area beneath the curve being a region of depressed cardiac performance. This patient had impaired cardiac function throughout the labor and postpartum periods. The improvement with epidural analgesia is clearly demonstrated by the leftward shift in the point describing cardiac function. The dramatic shift to the right during the voluntary pushing of the second stage shows the depression in cardiac performance that occurred. Although cardiac performance began to improve 30 minutes following delivery (as shown by the left shift between 5 and 30 minutes postpartum), the administration of 20 mg of furosemide resulted in further improvement in ventricular function at 2 hours postpartum. Without further diuretic therapy, the patient's cadiac func-

tion approached that of the first stage of labor 9 hours postpartum.

Epidural analgesia in this case improved cardiac performance with a decreased PCWP, SVR, and increased cardiac output. Epidural anesthesia is therefore a highly effective technique for management of labor and delivery in parturients with the valvular lesions this patient had. Invasive monitoring of the patient was extremely valuable in following the changes in her cardiovascular status with epidural anesthesia and during labor. The deterioration in cardiac function of this patient with bearing down suggests that such efforts may be contraindicated in patients with regurgitant cardiac lesions. Fortunately, the second stage of labor was brief in this case, and the patient had only mild subjective symptoms of pulmonary venous congestion. A sustained second stage of labor in such an individual could progress to more flagrant decompensation. Therefore, cesarean delivery may be advisable in patients with regurgitant valvular lesions who fail to progress rapidly in the second stage. In view of the obvious improvements in cardiovascular performance with epidural anesthesia,

this technique would also appear to be the method of choice for operative delivery.

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Continuous Thoracic Epidural Anesthesia for Biliary Tract Surgery and for Postoperative Pain Relief in a Patient with Cystic Fibrosis

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The survival rate of patients with cystic fibrosis has markedly increased in recent years. The occurrence of biliary tract disease in patients with cystic fibrosis is high and increases further with advancing age. A case report of the use of continuous thoracic epidural anesthesia supplemented with endotracheal nitrous oxide for cholecystectomy and common bile duct exploration and use of continuous epidural analgesia for postoperative pain relief in a patient with cystic fibrosis is presented.

Case Report

A 22-year-old man was admitted with a chief complaint of severe epigastric pain, vomiting, and dyspnea. The patient had required numerous hospitalizations due to cystic fibrosis with severe pulmonary involvement since the age of 6 years. Physical examination showed an emaciated man weighing 45.6 kg. The patient complained of dyspnea in the sitting position. The chest was barrel-shaped and clubbing was present in all fingers. Bilateral rales and inspiratory and expiratory wheezing were heard over the entire lung field. The right upper quadrant of abdomen was tender. Abnormal laboratory tests included a white blood cell count 14,700/mm^3, and serum alkaline phosphatase 400 μ/ml, serum glutamic oxaloacetic transaminase of 60 μ/ml, and bilirubin of 6.4 mg/100 ml. Chest roentgenogram showed extensive bilateral fibronodular and emphysematous changes with prominence of pulmonary vasculature indicating pulmonary hypertension. Electrocardiogram showed

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right axis deviation and right ventricular hypertrophy. Intravenous cholangiography revealed a nonvisualizing gallbladder and several filling defects indicative of choledocholithiasis. Arterial blood gas tensions were P_{CO_2} 46.7 torr, P_{O_2} 50.5 torr, and pH 7.4 while breathing room air.

The patient was treated with intravenous fluids, intensive pulmonary therapy including postural drainage, intermittent positive pressure breathing and broncholytic and bronchodilating agents, antibiotics, and pancreatic enzyme. After 5 days, his pulmonary status had improved clinically as dyspnea disappeared and improvement was seen in the chest roentgenogram. Spirometric studies showed a tidal volume of 300 to 350 ml and forced vital capacity 1.75 L (47% of predicted 3.7 L for his age, weight, and height). Forced expiratory volume in 1 second (FEV$_1$) was 0.6 L, (18% of predicted value of 3.3 L), and FEV$_1$/forced vital capacity (FVC) $\times$ 100 was 34.2%. Spirometric studies had not been done on admission. Arterial blood gas tensions were P_{CO_2} 50 torr, P_{O_2} 50.7 torr, and pH 7.38 while breathing room air.

The patient was premediated with diazepam, 10 mg intramuscularly, 1 hour before placement of a 20-gauge epidural catheter via a Touhy-Huber needle at the T8–9 space; the tip of the catheter was advanced 3 cm cephalad beyond the tip of needle. After a test dose of 3 ml, bupivacaine 0.75%, 12 ml, was injected. After levels of anesthesia between T-5 and T-12 were established, tracheal intubation was performed with the aid of d-tubocurare, 3 mg; sodium thiopental, 150 mg; and succinylcholine, 60 mg, intravenously. Nitrous oxide and oxygen were administered by controlled respiration with a humidifier in a semiclosed circle absorber system. Intravenous diazepam in intermittent doses totaling 7.5 mg was given during the procedure. Arterial blood gas tensions were monitored via a radial arterial catheter to maintain proper respiratory gas exchange. Tracheobronchial toilet was performed as needed to remove thick yellowish secretions during cholecystectomy and common duct exploration which required 2 hours and 5 minutes. When nitrous oxide was discontinued at the end of the procedure, the patient was able to follow commands and to indicate that he felt pain. Bupivacaine 0.75%, 8 ml, was injected. In the intensive care unit, the patient's respirations were mechanically assisted through the tracheal tube. The patient was able to assist pulmonary therapy by helping in taking deep breaths, coughing, and changing positions for pulmonary drainage. Six hours after surgery, one more dose of 8 ml of bupivacaine 0.5% was given. The patient required no further injections and the epidural catheter was removed. Twenty-four hours after surgery, when tidal volume and forced vital capacity were 350 ml and 1.6 L, respectively, the tracheal tube was removed.

On the 4th postoperative day, arterial blood gas tensions were P_{CO_2} torr, P_{O_2} 87 torr, and pH 7.42 while breathing room air. The patient required no further pain medication and was discharged on the 13th postoperative day at which

time arterial blood gas tensions were P_{CO_2} 40.3 torr, P_{O_2} 85.4 torr, and pH 7.40 while breathing room air.

Discussion

Cystic fibrosis is the most common lethal genetic pulmonary disease in childhood and adolescence in the United States. The incidence is approximately one in 1500 to 2000 births, and up to 5% of the general population are estimated to be carriers (1). In cystic fibrosis, the secretion of mucoglycoprotein in the tracheobronchial tree is increased due to hyperplasia and hypertrophy of mucus-secreting elements (2). Progressive pulmonary infection is the most important clinical problem (3). When infection occurs, the secretion becomes more difficult to remove because of increased viscosity (4). Mucociliary flow rate is also 5 to 10 times slower than in normal subjects of the same age (5). Improvement in the management of the pulmonary complications have played a major role in improving prognosis in this disease, and today mean survival rate has increased to 15 to 20 years, with a 50% survival rate beyond 26 years in selected centers (1, 3, 6, 7).

The incidence of gallbladder and biliary tract disease is high and increases with age in cystic fibrosis; 46.4% of patients with cystic fibrosis have nonfunctioning gallbladders and 11.9% have stones (8). Some of these patients will require surgery.

Most anesthetics, local or general, have a depressive effect on tracheal mucociliary flow rate as measured by cinebronchofiberoptic techniques, tantalum bronchography, or radioactive droplet techniques. Induction doses of 25 mg/kg of sodium thiopental do not depress mucociliary flow (9), but 40 mg/kg does depress mucociliary flow (10). Increasing the concentration of halothane from 0.6 to 1.2, to 1.8, and to 2.4 MAC progressively depresses mucociliary flow (11). Influrane in concentrations equal to 0.6, 1.2, and 1.8 MAC has a similar dose-dependent reversible depressant effect on mucociliary flow, as do combinations of anesthetics, such as nitrous oxide and halothane or nitrous oxide and morphine (12). Local anesthetics such as lidocaine 2% to 4%, procaine 0.5%, and mepivacaine 2% when applied into the tracheobronchial tree do not have a depressive effect on ciliary beating but in higher concentrations, significant depressions occurs (13–15).

In addition to changes in mucociliary transport associated with anesthetic agents, abdominal surgery, particularly upper abdominal surgery, is associated in normal individuals with adverse effects on respiratory

mechanics such as functional residual capacity (16–20), forced vital capacity (18, 19), vital capacity (18, 19), tidal volume (18, 19), residual volume (18), and closing volume (21).

With the combination of depressive effects of anesthetic agents on mucociliary transport and adverse changes in respiratory mechanics following abdominal surgery, the mucociliary transport is further depressed in the postoperative period, particularly in the areas of lobar or segmental atelectatis shown by pooling of insufflated tantalum powder for up to 6 days (22). Other factors influencing mucociliary transport mechanisms include body temperature (23); temperature of inspired gases (24, 25); state of hydration, oxygen, and carbon dioxide administration (26, 27); tracheal intubation; premedication; infection; and effectiveness of coughing as affected by pain or other factors such as chronic obstructive pulmonary disease.

As mucociliary clearance is an important pulmonary defense mechanism against infection, general anesthesia using inhalation or intravenous agents may be deleterious to the patient with cystic fibrosis undergoing surgical procedure. The goals of anesthesia management in a patient like ours should include: (a) avoidance of anesthetics that depress mucociliary transport, (b) liquefaction and elimination of mucoglycoprotein secretions from the respiratory tract with tracheobroncheal toilet, (c) provision of postoperative pain relief adequate to prevent deterioration of respiratory mechanics, (d) postural drainage, and (e) ambulation as early as possible. Previous studies have emphasized the importance of preexisting respiratory disease in determining the incidence of postoperative respiratory complications, though there appears to be no difference in the incidence of postoperative respiratory complications in patients given general and those given spinal anesthesia (28, 29). However, in our patient, continuous thoracic epidural anesthesia provided excellent anesthesia and muscle relaxation without use of muscle relaxants for surgery, as well as excellent pain relief in the postoperative period, hence making it possible to restore respiratory function to the preoperative level more rapidly without use of narcotics (30, 31). If our patient had required pain relief after removal of the epidural catheter, intercostal block would have been provided.

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High-Frequency Positive-Pressure Ventilation for Tracheal Reconstruction Supported by Tracheal T-Tube

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High-frequency positive-pressure ventilation (HFPPV) was first described by Oberg and Sjöstrand (1), who demonstrated in animals that ventilation and oxygenation could be adequately maintained with much lower tidal volumes and higher respiratory rates than conventionally used. This method of ventilation was studied in humans by Jonzon et al (2) and was first reported during clinical anesthesia and surgery by Heijman et al in 1972 (3).

HFPPV is one of two types of high-frequency ventilation; the other is high-frequency oscillation. They differ in the tidal volumes and respiratory rates used. In HFPPV, tidal volumes that approach the anatomic dead space (50 to 250 ml) are delivered at rates of 1 to 10 Hz (60 to 600 breaths/min); alveolar ventilation with this technique is thought to be accomplished by a combination of convection and improved gas diffusion. In high-frequency oscillation, lower tidal volumes (5 to 50 ml) are delivered at rates of 10 to 100 Hz (600 to 6000 breaths/min); alveolar ventilation during high-frequency oscillation is thought to be accomplished by acceleration of gas diffusion and collateral intra-alveolar ventilation (4-7).

The high velocity of the small tidal volumes deliv-

ered at a rapid respiratory rate generates a turbulent gas flow and irreversible gas diffusion. Gas mixing is improved during high-frequency ventilation with uniform gas distribution independent of regional time constant. The airway pressure during high-frequency ventilation has been shown to be continuously positive and functional residual capacity has been shown to be increased. Intrapleural pressure has also been shown to be continuously negative, with minimal changes in venous pressure, pulmonary vascular resistance, and cardiac output (8, 9).

The T-shape triple-lumen tracheostomy tube was introduced by Montgomery in 1965 (10). The intratracheal portion (intraluminal limb) of the tracheal T-tube has been used as a stent to maintain the patency of the upper airway in patients with subglottic and upper tracheal stenosis. The intraluminal limb also maintains the circumference of the airway and supports the tissue graft applied during the reconstruction of the larynx and cervical trachea. The tracheostomy portion (extraluminal limb) of the tracheal T-tube can be occluded with a plug in patients with adequate upper airway to restore the functions of the larynx (cough and phonation) (11-16). Because of the problems in establishing an adequate airway through a tracheal T-tube using conventional methods of ventilation during anesthesia and resuscitation, we report the application of HFPPV through a small catheter during tracheal reconstruction with placement of a Montgomery tracheal T-tube.

The evaluation of HFPPV was approved by our Review Board for Human Investigation and informed consent was obtained from the patient.

Case Report

A 55-year-old man with severe stenosis of the cervical trachea was admitted for tracheal resection. The tracheal stenosis was the result of accidental inhalation of a sulfur-containing compound in 1946, which was treated by tracheostomy for 5 months. However, the stoma failed to heal and was closed with a skin graft. During the year before admission, he complained of progressive shortness of breath during exertion, which was relieved temporarily (3 to 4 weeks) by bronchoscopic tracheal dilation. Six months before admission he underwent a bronchoscopic resection of mural cartilage, with unsatisfactory results. He also had a history of hypertension and irregular heart beat which did not require treatment. Physical examination revealed a tracheostomy scar and a fixed tracheal mass; pulse was 84 beats per minute (irregular), blood pressure 140/80 mm Hg, and electrocardiogram (ECG) showed left bundle branch block with multiple ventricular premature beats. Tomo-

grams of the trachea showed stenosis of 60% of its expected diameter for a segment of 5 cm, just below the laryngeal ventricle, together with asymmetry of the piriform sinuses.

Anesthesia. Atropine, 0.4 mg, was given intramuscularly for premedication 1 hour before surgery. On arrival in the operating room, 14-gauge venous cannulas were placed in each arm for fluids and drug administration. A 20-gauge cannula was also placed in the left radial artery. After preoxygenation and establishment of continuous ECG and blood pressure monitoring, anesthesia was induced with lorazepam, 4 mg; thiopental, 150 mg; and fentanyl, 0.05 mg/kg. Muscle relaxation was obtained with pancuronium bromide, 0.15 mg/kg. After laryngoscopy, the trachea was intubated with a 2-mm i.d., 45-cm presterilized catheter for HFPPV. A fine metal stylet was placed inside the catheter to improve rigidity and facilitate intubation.

The HFPPV catheter had a single hole at the distal tip, and the proximal end was fitted with a metal adaptor to prevent leakage or disconnection during the use of HFPPV. The proximal end of the catheter was connected to the output tubing of a high-frequency ventilator.

The high-frequency ventilator we used is based on a pneumatic valve system, powered independently by oxygen at 50 psi, which controls a pneumatic solenoid valve. The frequency range is between 10 to 3000 breaths per minute. Insufflation time is controlled independently between 0.01 to 1 second. The solenoid valve functions as an interrupter to the HFPPV gas output. Driving gas pressure (DGP) is controlled by a manual one-stage reducing valve. The ventilator and the catheter were designed in our department by the senior author (N.E.).

HFPPV of both lungs through the catheter with 100% O_2 was used initially at a frequency of 150 breaths per minute, DGP of 15 psi, and insufflation time percent of 40%. With these settings the mean Pa_{O_2} was 446 mm Hg (438 to 450 mm Hg) and mean Pa_{CO_2} was 49 mm Hg (47 to 55 mm Hg). DGP was increased to 20 psi. This increased the mean Pa_{O_2} to 510 mm Hg (485 to 530 mm Hg) with no significant change of mean Pa_{CO_2} of 48 mm Hg (46 to 52 mm Hg). Further increase of DGP to 25 psi provided adequate CO_2 elimination and oxygenation; mean Pa_{CO_2} was 43 mm Hg (38 to 45 mm Hg), and mean Pa_{O_2} was 517 mm Hg (492 to 545 mm Hg). Blood gas tensions were measured every 5 minutes, and DGP was increased by 5 psi at 30-min intervals. Other monitoring included neuromuscular transmission, temperature, urine output, and central venous pressure.

Surgical Procedure. A transverse skin incision was made 2 cm above the sternal notch. The trachea was found to be scarred and adherent to a large fibrous mass extending down into the mediastinum. Because of the difficulty in identifying the left recurrent nerve, it was feared that tracheal resection and anastomosis would sacrifice the left recurrent nerve, causing cord paralysis. Alternatively, it was decided to reconstruct and widen the trachea with a hyoid bone graft supported with a tracheal T-tube.

The trachea was incised longitudinally in the midline

from the 2nd to the 5th cartilage rings. The distal end of the HFPPV catheter was pulled out through the tracheal incision and passed through the intraluminal (intratracheal) lumen of an 8-mm i.d. tracheal T-tube (Fig 1). The catheter and the T-tube were placed inside the trachea and HFPPV of both lungs was continued. A hyoid bone graft was mobilized with its blood supply and wedged between the edges of the tracheal incision. The T-tube provided support and stability for the bone graft (Fig 2).

At the completion of surgery (7 hours) HFPPV was continued through the catheter in the postoperative period rather than relying on reversal of the large amounts of pancuronium (20 mg) and fentanyl (3.5 mg) used.

Postoperative Period. The patient received HFPPV during transit to the surgical intensive care unit. The HFPPV ven-
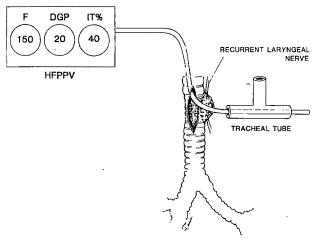
FIG 1. HFPPV catheter placed inside intraluminal limb of tracheal T-tube. Abbreviations used are: F, frequency; DGP, driving gas pressure; IT%, insufflation time present.
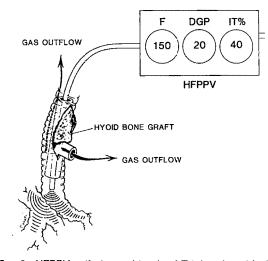
FIG 2. HFPPV catheter and tracheal T-tube placed inside trachea. Hyoid bone graft is supported by T-tube. Extraluminal limb and open glottis function as port for HFPPV gas outflow. HFPPV parameters are shown in top box. Abbreviations are the same as in Fig 1.

tilator was powered and supplied by oxygen from a portable tank, which was fitted with a special pin-index outlet valve.

HFPPV was continued in the surgical intensive care unit at a frequency of 150 breaths per minute, DGP 25 psi, insufflation time percent 40%, and Fi_{O_2} 0.5. After 2 hours, the patient was breathing spontaneously and was responding to verbal commands. Weaning from HFPPV was started by gradual reduction of the DGP by 5 psi every ½ hour. The other parameters of HFPPV were not changed. The patient was successfully weaned and the catheter removed 4 hours after admission to the surgical intensive care unit. Blood gas tensions were measured frequently to assure adequate ventilation and oxygenation during the period of weaning. The changes in pH, Pa_{CO_2}, and Pa_{O_2} during the different parameters of HFPPV used during and after surgery are shown in Figs 3 and 4.

The patient's postoperative course was uncomplicated. He was discharged on the 7th postoperative day with the tracheal T-tube in place. The tracheal T-tube was removed after 6 months and the stoma was successfully healed.

Discussion

The ideal method of ventilation during anesthesia for surgery involving the major airways should provide adequate alveolar ventilation and oxygenation during the period of resection and reconstruction of the airway. It should provide maximal surgical access
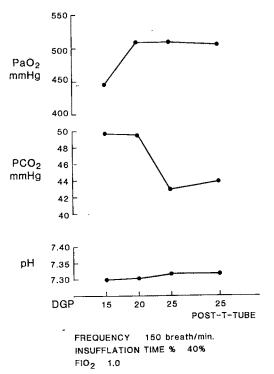
FIG 3. Pa_{O_2}, Pc_{O_2}, and pH during HFPPV at different DGPs. Notice improvement of CO_2 elimination by increasing DGP to 25 psi, and minimal effect of placing T-tube in trachea.
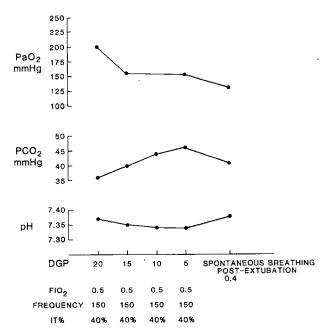
FIG 4. Pa_{O_2}, Pc_{O_2}, and pH during weaning from HFPPV. DGP was decreased 5 psi every ½ hour.

to the circumference of the open airway for perfect anatomic alignment and an airtight reconstruction. Our choice of HFPPV through a small catheter was based on the original surgical plan to resect the stenotic portion of the cervical trachea. The change of surgical plan to reconstruct the trachea with a hyoid bone graft supported by a tracheal T-tube showed another advantage of HFPPV.

Because of the design and shape of tracheal Montgomery T-tubes, it is difficult to establish an adequate airway for the administration of conventional mechanical ventilation as with conventional cuffed tracheostomy tube (17, 18). The use of the extraluminal limb as an airway for the delivery of the large tidal volume during conventional ventilation is associated with a large gas leakage through the open upper intraluminal limb and around the uncuffed tracheal T-tube. This leakage will prevent the generation of adequate positive airway pressure which is essential for convective (bulk) flow ventilation. Two techniques have been described to permit the use of conventional intermittent positive pressure ventilation (IPPV) through the external extraluminal limb. The external lumen of the T-tube can be fitted with a standard 15-mm adaptor and connected to the conventional IPPV anesthesia circuit. However, adequate alveolar ventilation can only be achieved after occlusion of the superior part of the intraluminal limb to minimize the escape of the delivered tidal volume through the open

glottis. In one technique this has been accomplished with a Fogarty embolectomy catheter introduced through the extraluminal limb into the upper intraluminal limb. In the other technique, the glottis and the upper limb of the T-tube are occluded with a tight pharyngeal pack. IPPV can also be administered through the intraluminal limb of the tracheal T-tube. The technique of translaryngeal intubation of the upper intraluminal limb with a Cole tube was described in a pediatric patient. Once the airway is established, occlusion of the extraluminal limb will allow the use of IPPV (19, 20).

We believe that these maneuvers and techniques are cumbersome, difficult to apply, and perhaps dangerous. They can, for example, totally obstruct the airway and prevent alveolar ventilation. Besides, their application during tracheal reconstruction and placement of the T-tube can impair surgical access and complicate the surgery.

The tracheal T-tube can be utilized to maintain the airway during anesthesia in patients with T-tube. Nonetheless, the choice of anesthetic techniques is limited by the mandatory maintenance of adequate spontaneous breathing. The recommendation that the T-tube be replaced with a standard tracheostomy or endotracheal tube before the administration of general anesthesia and mechanical ventilation may prove harmful in patients with recent tracheal reconstruction.

Injector jet ventilation through a small catheter can be used as a method of ventilation during tracheal reconstruction with a tracheal T-tube. However, the large tidal volumes used impair pulmonary and systemic circulations, and the negative pressure generated by the jet suctions blood and debris into the trachea and lower airways. These disadvantages limit the value of this technique during major airway surgery (21, 22).

Alternatively, we found that HEPPV through a 2-mm i.d. catheter provided adequate alveolar ventilation and oxygenation during tracheal reconstruction and the placement of a tracheal T-tube. The small catheter provided optimal surgical access during tracheal reconstruction and accommodated the change in surgical plan. The placement of the tracheal T-tube required only the simple maneuver of placement of an HFPPV catheter through the intraluminal limb. During HFPPV, the T-tube and the open trachea functioned as expiratory ports for the continuous outflow of gas; this prevented the contamination of the lower trachea and bronchi with blood and debris.

HFPPV through a small catheter can be used to provide controlled ventilation during anesthesia in patients with a tracheal T-tube. Translaryngeal intubation of the intraluminal limb and trachea can be easily accomplished with the small HFPPV catheter. Alternatively, a HFPPV catheter can be introduced through the extraluminal limb, gently flexed upward, to direct the catheter to lie above the carina. A smaller catheter or a cannula can be used in pediatric patients. This technique can be used to provide respiratory support during resuscitation of patients with tracheal T-tubes. The use of HFPPV after surgery for respiratory support and weaning during the recovery from anesthesia showed another advantage of this technique. HFPPV was reported to inhibit spontaneous breathing in some patients when a DGP greater than 35 psi was used (23). Nonetheless, HFPPV provided adequate ventilation and oxygenation with no impairment of return of spontaneous breathing and was well tolerated by our patient.

We believe that HFPPV through a catheter is an ideal technique for the anesthetic management of patients having tracheal reconstruction and patients with tracheal T-tubes.

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letters

TO THE EDITOR

Bicitra Is 0.3 Molar Sodium Citrate

To the Editor:

I was interested in the study performed by Eyler et al (1) in which they compared Mylanta, a particulate antacid, and Bicitra, a soluble antacid, both as antacids and as pulmonary irritants. Our pharmacy has been reluctant to prepare a sodium citrate solution as a soluble antacid for use in our obstetric suite so we have been seeking a commercial preparation with demonstrated effectiveness. Their study suggests that Bicitra may well be a suitable alternative to particulate antacids. There is difficulty, however, when one tries to compare their results with those of others who have studied sodium citrate. Previous investigators have utilized 0.3 M sodium citrate (2) whereas Eyler et al state that they evaluated 1 M sodium citrate diluted to half strength. The molecular structure of sodium citrate and the concentration of this dihydrated compound in Bicitra reveals that they did not, in fact, evaluate 1 M sodium citrate. The molecular weight of dihydrated sodium citrate is 294. Bicitra contains 100 g of sodium citrate/1000 ml, i.e., 100 g/294 g or 0.34 M. Therefore, the concentration of sodium citrate in Bicitra is equivalent to that used by others and the concentration studied by Eyler et al was in reality 0.17 M, approximately half the strength evaluated by others. This confusion may have occurred because sodium citrate contains three atoms of sodium per molecule. Thus, a one third molar solution is actually one normal (N) and is indeed 1 M for sodium ion. This error does not detract from their results, which emphasize the potency of sodium citrate as an antacid and its apparent decreased potential for inducing lung injury if

aspirated. The primary emphasis must continue to remain, however, on rapid and skillful protection of the airway with a cuffed endotracheal tube for patients at risk for aspiration of gastric contents.

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Nonparticulate Antacids

To the Editor:

Prophylactic administration of antacids has been used to alleviate the more harmful effects of the aspiration of acidic gastric contents. However, in dogs, particulate antacids can produce a severe bronchopneumonia (1). The paper by Eyler et al (2) documents again the more severe pathologic changes after the aspiration of a particulate antacid. A nonparticulate antacid, sodium citrate, has been shown to be safe and to decrease effectively gastric acidity (3, 4). The pH of a 0.3 M sodium citrate solution is approximately 8.4. The pH of Bicitra, the nonparticulate antacid containing sodoim citrate and citric acid and evaluated by Eyler et al (2), is approximately 4.2. The large difference in pH may not be clinically significant. Although Bicitra has been shown to produce minimal pulmonary pathology after aspiration, whether this agent

effectively decreases gastric acidity needs to be demonstrated before it is used prophylactically.

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Electrochemical Skin Burn after Transcutaneous Electronerve Analgesia

To the Editor:

Temporary relief of pain by transcutaneous electrical nerve stimulation (TENS) has been observed by many investigators (1-3). This method has been used for relief of postoperative pain by intracutaneous implantation of metallic suture material (Ethicon 4-0) into the skin (4). We modified this system of postoperative TENS by using Michel clips attached to electrodes of a transcutaneous nerve stimulator. These electrodes are then attached to both ends of the surgical incision. We obtained good pain relief in many

patients, but we want to report one case with an unusual complication, a skin burn.

Total abdominal hysterectomy was performed under general anesthesia through a Pfannenstiel incision in a 62-year-old woman who had normal biochemical blood tests and a normal physical examination. TENS was applied to the skin with frequency change from 50 to 100 Hz, pulse duration 0.5 msec, voltage output 80 V, and maximum single pulse current 40 mamp, in continuous stimulation for 48 hours, without postoperative pain. At the site of the Michel clips there developed, however, signs of third degree burns (1.5 x 1 cm) and on the clips were electrical corrosion and salt deposits.

Our explanations for this complication are: (a) The copper electrodes were attached to stainless steel. These two different metals separated by a conducting fluid from the incision and from the skin formed a battery, although one of low voltage. Perhaps there was an electrochemical reaction between these two metals. (b) At a junction between the metal and the skin, rectification of the TENS voltage applied could have taken place, resulting in a DC voltage. This can cause electrolysis of saline with resulting generation of sodium hydrochloride and hydrogen at the cathode and chlorine and oxygen at the anode. (c) The use of electrical stimulation continued for too long a time.

We conclude that electrical stimulation during TENS should be applied intermittently. The best way of achieving this is to have the electronerve analgesia applied by the patient himself according to his needs. The electrodes should be connected directly to the skin, and the skin should be completely dry and clean. After this episode, we changed our method accordingly without again encountering this complication.

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Aortic and Mitral Valve Replacement after Sickle Cell Crisis

To the Editor:

A 30-year-old black woman, 162 cm tall and weighing 50 kg, with a history of rheumatic heart disease and sickle cell anemia, was scheduled for aortic and mitral valve replacement because of severe aortic and mitral regurgitation and pulmonary hypertension. Thirteen days before surgery she was admitted because of a sickle cell crisis. After this crisis resolved, the patient underwent a partial exchange transfusion 2 days before surgery with 1150 ml of washed red blood cells. This resulted in a hemoglobin S level of 50% and a hemoglobin A level of 45%. A second partial exchange of 1260 ml was carried out the day before surgery, elevating the hemoglobin A to 73% and decreasing hemoglobin S to 25% with a hemoglobin level of 10.6 g%.

A review of the literature revealed no reports of cardiopulmonary bypass in a person with SS hemoglobin. A goal of 60% to 70% hemoglobin A was set on the basis that partial exchange transfusion, until this level of hemoglobin A is achieved, has been proposed as therapy for sickle cell crises and as a means for prevention of crises during anesthesia for major surgery (1-3).

It is possible to do partial exchange transfusions before surgery or during surgery after cannulation for bypass. Exchange before surgery was chosen for our patient for the following reasons: (a) None of the patient's own plasma or clotting factors would be lost; (b) The transfused blood would

have time to increase its 2,3-diphosphoglycerate levels and oxygen carrying ability before surgery; (c) The number of erythrocytes with hemoglobin S would be greatly decreased. As they are the cells that adhere abnormally to the endothelium, their adherence correlates with clinical severity (4); (d) Changes in blood volume would be minimal and the patient would have time to adjust to the changes; and (e) The protection afforded by partial exchange transfusion would be present during induction of anesthesia and during surgery before insertion of cannulae before cardiopulmonary bypass.

At the time of surgery the patient was prepared by insertion of intravenous lines and arterial and Swan-Ganz catheters. Anesthesia was induced after administration of 30 mg/kg of methylprednisone (Solu-Medrol) with fentanyl, diazepam, and lidocaine. Relaxation was obtained with pancuronium and metocurine. Except for hypothermia to 26°C during bypass, the general principles of care for sickle cell patients, including avoidance of acidosis, dehydration, and hyperventilation, were followed (2, 5).

The cardioplegia solution and the pump prime solution were our standard, except that blood and albumin were added to the pump prime solution. Cardiopulmonary bypass lasted approximately 2¾ hours, during which Bjork Shiley valves were placed in the aortic (#23) and mitral valve (#29) locations. Hemoglobin levels were approximately 8 g%/ml during bypass, increasing to 8.8 near the end of the procedure.

The bypass and post-bypass periods were uneventful. The patient was extubated the following morning, at which time the hemoglobin S concentration was 3% and hemoglobin A 97%. She was discharged from the intensive care unit later that day and discharged from the hospital 8 days later.

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Variability of Cerebrospinal Fluid Density

To the Editor:

I would like to call attention to an apparent inaccuracy in a conclusion made in the paper by Levin et al (1) based on a probable misquotation.

Levin et al wrote that Davis and King (2) "reported a density range of 0.9990 to 1.0030 g/ml at 37°C." Levin et al then concluded in part that the true range of human cerebrospinal fluid (CSF) density values is probably narrower than our "0.9990 to 1.0030 g/ml."

At 37°C the CSF densities that we measured ranged from 1.0006 to 1.0013 g/ml. We also calculated a 99.73% confidence limit of 0.9998 to 1.0022 g/ml. We did not report a wider density range of 0.9990 to 1.0030 g/ml at 37°C.

All of the confidence limits given by Levin et al are the more inclusive 95%, and their standard deviations (SD) appear to be derived from nine CSF samples at 37°C and eight CSF samples at 23 to 25°C. Our preferred SD values, merely ± 0.0001 g/ml larger, were based on the series of 150 CSF samples studied by Wolman et al (3). Although we did measure with precision at 37 and 25°C, we primarily confirmed the results of larger series reported by others, transforming their compound specific gravity values to the more fundamental density values and applying statistical analyses to their results.

When the misquotations are corrected and expressed with similar confidence limits, I believe that the normal variability range reported by Levin et al and that reported by ourselves will be recognized to be similar.

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San Francisco, CA 94116

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Liquid Crystal Thermometry

To the Editor:

Vaughan et al (1) demonstrated that contacting liquid crystal temperature trend monitors provide imprecise thermometry under hypothermic clinical conditions; this has always been a limitation of simple contact thermometry. Surface temperature is almost totally a function of cutaneous blood flow and not the metabolic rate of the underlying tissue; it is further modified by environmental factors (humidity, ambient temperature, wind speed) and any perturbations caused by the contacting probe itself. Their information would have been more helpful had they taken into account ambient temperature, relative humidity, and air handling within their recovery facility. Also, because liquid crystal monitors require interpretation in determining temperature, failure to "blind" the observer to the tympanic membrane temperature introduces experimental bias.

In quoting the work of Benzinger (2), they state that tympanic membrane temperature is an accurate and precise indicator of core temperature. The authors use the term "core" temperature repeatedly without defining the term. Although it is conceptually convenient to speak in terms of core and shell temperatures when discussing heat transfer, it is not something that can be clinically monitored unless defined. Traditionally intracardiac blood temperature has been the "gold standard" for core temperature; deep esophageal temperature is the second best method. Tympanic membrane temperatures, however, are not always identical with core temperatures. Cabanac et al (3) have shown an increasing gradient between deep esophageal and tympanic membrane temperature where facial cooling is instituted.

Hammel et al (4) did not show a "reasonable correlation between hypothalamic and rectal temperatures" as claimed by Vaughan et al. Rather, Hammel et al demonstrated in monkeys and dogs, not humans, that the set point for temperature regulation is decreased by increasing skin or extrahypothalamic (rectal) temperatures and increased by decreasing skin and extrahypothalamic temperatures. There are no thermal receptors in the rectum and no clear relationship exists between rectal temperature and either sweating or vasomotor tone. Indeed, the Benzinger article, referenced by the authors and 6 years more current than Hammel, showed that rectal temperatures and tympanic membrane temperatures often differ by wide margins.

Core (intracardiac) temperature can, however, be monitored reliably and accurately using a noninvasive method (5) that makes use of the zero heat flux principle. This method uses a contacting cutaneous probe that creates a zone of no heat flux between deep body structures and the skin surface. Although simple to use, it does require line-operated (120 V) electronics and costs several thousand dollars.

Liquid crystal temperature trend indicators are not thermometers; that they indicate a change from base line and the need for more accurate thermometry is sufficient. What is important is that these liquid crystal monitors rapidly detect a trend. Vaughan et al (1) feel that "the question of whether liquid crystal thermometry may be useful in clinical situations to diagnose or follow trends with extreme temperature change (e.g., malignant hyperthermia) remains unanswered," but our paper (6) successfully showed that they will at least rapidly detect acute increases in body temperature, their objection to our use of linear regression analysis notwithstanding. In preparation for an

anesthetic, the selection of appropriate temperature monitoring is a clinical judgement best reserved for the individual anesthesiologist. Liquid crystal monitors should not supplant accepted clinical thermometry practices, but rather fill those monitoring voids (e.g., brief outpatient anesthetics) where thermometry is rarely practiced.

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2. Benzinger TH. Clinical temperature: new physiological basis. JAMA 1969;209:1200–6.
3. Cabanac M, Caputa M. Open loop increase in trunk temperature produced by face cooling in working humans. J Physiol (Lond) 1979;289:163–74.
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To the Editor:

We appreciate the interest generated by our recent article (1) and the opportunity to respond.

For any study, a discussion of validity must address whether the instrument [tympanic membrane sensor (TM)] actually measures the concept in question (core body temperature). Our definition of core temperature (TM) does appear in the abstract of our article. Moreover, the use of the word "core" subserves a conceptual convenience need.

Although temperature measurements taken at more central locations of body circulation (intracardiac and esophageal) have been accepted as core measurements and are indirectly assumed to reflect mean body tissue temperature, routine use of these

monitoring techniques in the recovery room is not reasonable. Moreover, such techniques may not be well tolerated by the emerging, postanesthetic adult. Rectal temperature has been accepted as the traditional measuring site of core temperature before investigations by Benzinger and others who showed a disparity between esophageal and rectal temperatures (2). Studies not originally cited by us, but ones that lend clinical support to the correlation of TM with esophageal temperature measurements are those by Webb (3) and Benzinger (4). For example, in 35 subjects who underwent saphenous-vein bypass procedures for aortocoronary surgery, Webb found that TM closely parallels simultaneous temperature measurements made in the esophagus. A limitation of this study is that two cases were cited rather than complete data with mean and SEM values for each site at each time point. Nevertheless, Webb's suggestions support similar results reported by Benzinger. Thus, in the recovery room, we chose TM temperature to be compared with the "shell" or skin temperature [liquid crystal adhesive temperature strip (TS)].

The paper by Cabanac and Caputa (5) cited by Lees, although interesting, addressed facial heat dissipation during muscular work in a cold environment. We question the clinical relevancy of assuming that differences between esophageal and TM measurements in five healthy, exercising male adults can be extrapolated to inactive, recovering, postanesthetic adults.

The use of unblinded observer to strengthen our study design is a valid point. Such a study design would, however, have required two trained observers recording separately the simultaneous TM and TS observations. Economic considerations dictated our final design.

We agree with Lees that "liquid crystal monitors should not supplant accepted clinical thermometry practice." Unfortunately, although TSs were designed to track core temperature changes, i.e., trend indicators, they are also used as a reliable index of core temperature. The purpose of our study was to determine whether TS could be a reliable trend indicator of core temperature in recovering

postanesthetic adults. Trends are measured over time. Based on correlation coefficients generated from independent observations over time, our data comparing TM with TS support the premise that temperature strips are not reliable trend indicators. Although it may be true that liquid crystal monitors will detect initial or intermittent "acute" increases in body temperature, we disagree that data presented in the article by Lees et al (6) support that conclusion. Linear regression requires independence of observation; otherwise, the analysis is invalid. Conclusions drawn from violation of statistical assumptions remain questionable at best.

Finally, as requested by Lees, we are pleased to supply additional information that may be relevant for clinical interpretation of our article. During data collection, all subjects remained in a relatively stable recovery room environment. Ambient temperature (mean ± SEM) was 21.6 ± 0.03°C, relative humidity was 55% ± 0.12%, and approximated air exchange was 5 to 12 times per hour.

We thank Lees for his interest, observations, and critique, and trust this dialogue clarifies rather than confuses.

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Pulmonary Capillary Wedge Pressure

To the Editor:

Kaplan and Wells' recent study (1) and Kaplan's letter (2) expand our understanding of left ventricular (LV) diastolic properties and cardiac monitoring. Kaplan et al (1, 3) have demonstrated the usefulness and need for careful observation of pulmonary capillary wedge pressure (PCWP) tracings during coronary artery revascularization.

Kaplan and Wells (1) assume that acutely decreased LV compliance, as evidenced by sudden large A and V waves of the PCWP tracing, is representative of myocardial (subendocardial) ischemia. Decreased LV compliance may be associated with subendocardial ischemia, as described, but other factors also govern LV diastolic pressure-volume relationships.

Alderman and Glantz (4) have demonstrated altered LV diastolic pressure-volume curves in patients with and without coronary artery disease after angiotensin infusion. These patients demonstrated increased LV

diastolic "stiffness" ($\Delta P/\Delta V$) without evidence of myocardial ischemia. Mitchell et al (5) and others have shown that rapid heart rates in dogs may alter LV diastolic pressure-volume curves by allowing only incomplete LV relaxation and thus increased diastolic stiffness, and therefore, possibly increased intracardiac pressures. In patients with coronary artery disease, a disparity between left atrial pressure and LV end diastolic pressure may appear during tachycardia (6). At these rapid heart rates, a superimposition of sudden large A and V waves in the left atrial pressure tracing has been observed with simultaneous decreases in the LV end-diastolic pressure (7). Perhaps this divergence of pressures is due to atrial contraction against a closed mitral valve. Thus, it appears that acutely abnormal PCWP tracings may exist without concomitant myocardial ischemia.
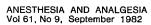
During anesthesia and surgery, both endogenous and exogenous vasoactive substances may act to alter LV diastolic pressure-volume relationships, as evidenced by abnormal PCWP tracings. As Kaplan points out, a sudden abnormal PCWP tracing is

an important hemodynamic event and requires prompt treatment.

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book
REVIEWS

Respiratory Failure in the Child, edited by G. A. Gregory, New York, Churchill Livingstone, 1981, 205 pp, $32.50.

The strength of this book lies in its uncommon focus on common pediatric problems. The pediatric literature is replete with basic information concerning illness associated with respiratory distress. However, because the range of severity of disease in these conditions is broad, and severe respiratory dysfunction or outright respiratory failure relatively uncommon, most texts give elaborate attention to the milder end of the spectrum. They emphasize outpatient management or the needs of less seriously ill hospitalized patients. Most content themselves with an acknowledgment that respiratory failure may occur, but offer little to guide the clinician who sees sicker children.

This volume picks up where others leave off, with emphasis on the pathophysiology and treatment of asthma, aspiration syndromes, congestive heart failure, and chronic lung disease in their extreme. Overall, it is a well organized tour through clinical material that represents a large fraction of pediatric intensive care. The initial chapter on diagnosis of respiratory failure is far too basic, but other chapters provide a useful overview of intubation, mechanical ventilation, monitoring, and adverse sequelae of therapeutic intervention.

The chapters on specific clinical disorders consolidate information on pathophysiology and an approach to treatment not readily found elsewhere in one place. Although no chapter can be considered a step-by-step guide to management, each pro-

vides an extensive theoretical rationale for a practical approach to caring for a child unfortunate enough to manifest severe respiratory dysfunction. The chapters on status asthmaticus and respiratory failure of cardiac origin are the most intellectually satisfying in their effective synthesis of clinical, physiologic, and pharmacologic data.

The book will be of greatest value to those training in pediatric intensive care, but it will also serve more experienced clinicians as a resource for teaching. Extensive current bibliographies contained in each chapter will save many trips to the library. Academic referral pediatricians, whose patients are disproportionately represented on the severe end of the spectrum, and pediatric anesthesiologists, who must often care for these children in the midst of their illness, will also find it useful.

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Catheterization Techniques for Invasive Cardiovascular Monitoring, by C. D. Blitt, Springfield, IL, Charles C Thomas, Publisher, 1981, 144 pp, $28.75.

Invasive cardiovascular monitoring has become common practice in the anesthetic management of the critically ill adult and child. This well organized, small book reviews in detail the indications, technique, equip-

ment, and complications in the use of arterial catheters, central venous pressure catheters, and pulmonary arterial catheters. The book is, in general, well written but contains some occasional redundancies. The reader wonders if the author could not have uniformly called "lines" catheters to help remove jargon from medical writing. More important, however, the descriptions of catheter insertion techniques are clear, simple, and straightforward. This certainly reflects Dr. Blitt's vast teaching and clinical experience. Likewise, the illustrations and photographs used to augment the text are clear and well labeled. For example, an ischemic hand can be distinguished from a nonischemic hand during performance of an Allen test in the black and white photographs.

During the first reading I thought the book was dogmatic—it is not. Unfortunately, Dr. Blitt has not added author citations or reference numbers to the text. This lack of citation in the text improves the readability, but makes it difficult to retrieve appropriate references from the extensive bibliography. The rationale for the use of a pulmonary arterial catheter in the critically ill patient (rather than central venous pressure catheters) is not developed in full detail. The experienced anesthesiologist will intuitively know why pulmonary arterial catheters are used in such patients but the novice could use more information. Many authors suggest "aiming" for the ipsilateral nipple during insertion of an internal jugular catheter. Therefore, it is somewhat disappointing that neither the illustrations nor the text makes this point clear. In addition, the pediatric anesthesiologist will be somewhat disappointed in this book as a teaching manual; the portion devoted to pediatric patients is severely limited. For example, there

is no information about umbilical artery or umbilical vein catheterization of the newborn. Likewise, the anesthesiologist performing his first arterial cutdown in a child, using this book as a guide, will find little help.

Clearly, there is a need for a book such as this as a teaching manual for anesthesiology residents. I doubt, however, if the experienced anesthesiologist would find this book of much value. The cost of this "little book" seems somewhat excessive, and this may limit its sale, which is unfortunate. Despite its minor flaws this is, indeed, a most useful teaching manual for anesthesiology residents.

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Ambulatory Anesthesia Care, International Anesthesiology Clinics, Volume 20, edited by S. W. Woo, Boston, Little, Brown and Co., 1982, 168 pp, $40.00/yr.

The message of this volume can be found in a remark made by Dr. Wong, one of its contributors, "a good ambulatory surgery program gives the anesthesiologist a very important opportunity to practice holistic medicine first and technical anesthesia skills second." The goal is to provide outstanding patient care, and in the case of the candidate for outpatient surgery the necessary role of the anesthesiologist becomes even more apparent.

The first two thirds of this volume are given to discussion of preoperative evaluation, the variety of surgery performed, the usefulness of specific anesthetic techniques, and the particular problems of some of the candidates for surgery as outpatients. Insofar as these authors discuss their experience with anesthesia for outpatients, they lend support to the claim of Dr. Loffer that "there is little question that outpatient anesthesia is a subspecialty and, as such, deserves special attention and regard." But as

the reader notes the particular recommendations made here for the anesthetic management of outpatients, it is clear that these recommendations could be and have been applied equally well to the majority of anesthetics administered to inpatients. The technical anesthetic skills required for safe and efficient care of outpatients are those required by any anesthesiologist attempting to restore consciousness with adequate analgesia to a patient as soon as possible following closure of a surgical procedure. Certainly the technical advances in anesthesiology that make rapid recovery of consciousness possible are a necessary requirement for the increased use of surgical facilities by outpatients, but the major currently limiting factors, and those that do differentiate the care of all outpatients from that of any inpatient, are administrative and economic.

The final third of this volume addresses these factors as they influence the function of freestanding surgical care facilities and hospital-based ambulatory surgical units. It is in this section that the practicing anesthesiologist may find some guidance for working out a modus vivendi with the needs of candidates for outpatient surgical procedures in a given medical environment. By addressing this situation, the anesthesiologist finds the opportunity to influence outside the operating theater aspects of patient care that are irrevocably tied to the intraoperative concerns of anesthetic practice. The anesthesiologist can have an important role in improving the delivery of surgical care to outpatients. Dr. Reed, Medical Director of the Surgicenter in Phoenix, Arizona, even believes that "the response to care in freestanding ambulatory surgical facilities has a significant message. . . . It is not government regulation that will bring about cost containment. Change that is initiated from within the medical profession itself will be responsible for maximizing quality of care while minimizing health care costs. Such changes will be effected by common-sense application of the knowledge and skills with which our medical training and practical experience have provided us."

The facts presented in this volume demonstrate that anesthesia for outpatient surgery can be administered

safely and efficiently, and that existing administrative conditions can be modified for the benefit of the patient. It is unclear what the effects of an increase in outpatient utilization of surgical facilities will be on practice patterns in referral and teaching institutions. Savings realized in an outpatient setting do not necessarily affect increasing costs in other areas of health care. There is a long path ahead before the benefits of increased outpatient surgery can be fully realized and its implications felt throughout the medical community. This volume marks the first decade of that experience.

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BOOKS RECEIVED

Preparation for Anesthesia, by A. J. Stevens, Baltimore, University Park Press, 1980, 453 pp, $29.95.

Seminars in Anesthesia, Volume 1, No. 1, edited by R. L. Katz, New York, Grune & Stratton, 1982, 70 pp, $34.00/yr.

Successful Management of Ambulatory Surgery Programs, edited by J. Jackson, C. Roach, M. Meyers, and L. Norins, Atlanta, American Health Consultants, 1981, 500 pp, $79.00.

Clinical Use of Mechanical Ventilation, by C. C. Rattenborg, Chicago, Year Book Medical Publishers, 1981, 363 pp, $16.00.

The Quality of Care in Anesthesia, by B. L. Grundy and J. S. Gravenstein, Springfield, IL, Charles C Thomas, 1982, 255 pp, $31.50.

Drugs of Choice 1982-1983, by W. Modell, St Louis, MO, CV Mosby, 1982, 809 pp, $49.50.

Anesthesia for Thoracic Surgery, by J.W.W. Gothard and M. A. Branthwaite, Boston, Blackwell Scientific Publications, 1982, 199 pp, $26.50.

Research Techniques in the Rat, by C. Petty, Springfield IL, Charles C Thomas, 1982, 368 pp, $36.75.

Lecture Notes on Fluid and Electrolyte Balance, by S. M. Willatts, Boston, Blackwell Scientific Publications, 1982, 308 pp, $15.95.

A Guide for Authors

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Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as described in Annals of Internal Medicine 1979; 90: 95-9, and Lancet 1979; 1: 428-30.

Type manuscripts on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in or 8½ by 11 in) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in). Use double spacing through-

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Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

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Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

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References. Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by arabic numerals (in parentheses). References cited *only* in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

Use the form of references adopted by the U.S. National Library of Medicine and used in *Index Medicus.* Use the style of the examples cited at the end of this section, which have been approved by the National Library of Medicine.

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References must be verified by the author(s) against the original documents.

Examples of correct forms:

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    Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687-90.

2. Corporate Author

    The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119-25.

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Books and Other Monographs

3. Personal Author(s)

    Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

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    American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

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    Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

    Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

7. Agency Publication

    National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

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Abbreviations. Define all abbreviations except those approved by the International System of Units for amount of substance, mass, length, time, temperature, electric current, and luminous intensity. Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

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ANESTHES
RESIDEN'
and
PROGR/
DIRECTO'

International An̲e̲s̲t̲h̲e̲s̲i̲a̲ Research Society

Publisher of ANESTHESIA and ANALGESIA

3645 Warrensville Center Road, Cleveland, Ohio 44122, U.S.A.

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SPONSORING ORGANIZATION: The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio. It serves the Specialty in two ways: (1) By publication of a monthly journal entitled "Anesthesia and Analgesia"; and (2) By sponsorship of an annual scientific ("Congress") meeting in March of each year. The I.A.R.S. is independent of, and has no affiliation or membership-exchange arrangement with any other anesthesia society or association:

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- ● a closed pop-off valve
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- ● a punctured ventilator bellows
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*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., et al.: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

References:
1. Bunker, J.P., et al.: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology 43:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

See following page for Brief Summary.

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of significance for cost-effectiveness as well as
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With characteristics that ensure ventilatory capacity and
a minimum of circulatory interference, your Emerson
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provide important benefits in routine cases as well.

*Sullivan, Saklad and Demers: "Ventilator Waveform and Gas Distribution" RESPIRATORY CARE 22:4:393.

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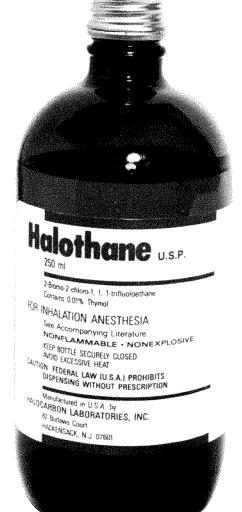
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A & A 9/82

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EDITORIAL

SCIENTIFIC ARTICLES

TECHNICAL COMMUNICATION

Contents

"Let's bring him out, now."

NARCAN® ampuls 0.4 mg/ml
naloxone HCl

rapidly reverses respiratory depression of narcotic-supplemented anesthesia

When partial or complete reversal is indicated, NARCAN® will quickly reverse narcotic-induced respiratory depression and help restore consciousness. The result? Your patient may be out of the recovery room and back in his own room sooner. Prompt restoration of the patient's protective reflexes reduces the risk of postanesthetic complications. Moreover, because the dosage of NARCAN can be titrated, the analgesic action of the narcotic can usually be preserved.

Response to NARCAN is usually evident within 2 to 3 minutes following intravenous injection and takes only slightly longer when given intramuscularly. For adults, to initially reverse narcotic respiratory depression, NARCAN should be administered in increments of 0.1 mg-0.2 mg I.V. at 2- to 3-minute intervals, to the desired degree of reversal (i.e., when adequate ventilation and alertness are achieved with satisfactory analgesia). It is important to monitor patients carefully and give repeated doses as needed since the duration of action of some narcotics may exceed that of NARCAN.

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NARCAN is a U.S. registered trademark of Endo Pharmaceuticals, Inc.
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(6)

The new Critikon Transcutaneous Gas Monitor.

Featuring the extraordinary interactive Display Panel.

Displays functions and asks questions to help you set operating parameters.

Tells you immediately what parameter is exceeded during an alarm condition.

PO₂ mmHg

TEMP °C   LIMITS   TE

5 8

4 4 . 0   CH 1   8 0   4 0   4 3

CHANNEL 1

HEATER POWER

2 8 1   MW

●ON
●OFF
2 MIN. OFF

ALARM

		YES	
1	2	3	↑ MENU
4	5	6	0 ITEM
7	8	9	↓ ENTER
		NO	

CRITIKON *Transcutaneous Gas Monitor* 8010

BRIEF SUMMARY:

© Critikon, Inc. 1982

Critikon
Transcutaneous
Gas Monitor

Indications:
Intended for use in transcutaneous blood gas monitoring.

Contraindications:
This device is not designed, sold, or intended for use except as indicated.

Limitations to patient selection:
Patients exhibiting severe edema or dermatitis may be inappropriate candidates for transcutaneous monitoring. Peripheral vascular shutdown such as that associated with deep shock may affect the displayed $tcPO_2$ readings. Trend data, however, may prove valuable in its recognition and management.

Warnings:
Exercise caution when interpreting readings of patient receiving gas anesthesia. Must not be used in presence of flammable anesthetics.

Cautions:
Do not apply sensor to previously used site if site exhibits effects of monitoring such as redness or inflammation. Use of external heat sources such as radiant heaters may affect sensor temperature, power usage, and consequently $tcPO_2$ values. Exercise caution when interpreting readings of patient exposed to external heat sources. Federal law restricts this device to sale by or on the order of a physician.

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(10)

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A Record of Success
PAVULON® nondepolarizing muscle relaxant
(pancuronium bromide injection)

BRIEF SUMMARY
(Please consult package insert for full prescribing information.)

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

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precise control...stability of heart rhythm...
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Ethrane® (enflurane)

DESCRIPTION

ETHRANE (enflurane) (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether) (CHF₂OCF₂CHFCl) is a nonflammable inhalation anesthetic agent. The boiling point is 56.5°C at 760 mm Hg. and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10} P = A + B/T$$

$$A = 7.967$$
$$B = -1678.4$$
$$T = °C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20°C is 1.3025-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C.

Enflurane is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary even in the presence of ultraviolet light. Enflurane is stable to strong base and does not decompose in contact with soda lime and does not react with aluminum, tin, brass, iron or copper. The partition coefficients of enflurane at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ETHRANE (enflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70 percent nitrous oxide—30 percent oxygen, and 1.17 in 30 percent nitrous oxide—70 percent oxygen.

[Remaining body text illegible due to image quality]

INDICATIONS AND USAGE

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Enflurane may be used to provide analgesia for vaginal delivery. Low concentrations of enflurane (see DOSAGE AND ADMINISTRATION) may also be used to supplement other general anesthetic agents during delivery by Cesarean section. Higher concentrations of enflurane may produce uterine relaxation and an increase in uterine bleeding.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).
Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.
Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

[Text largely illegible due to image quality]

PRECAUTIONS

[Text largely illegible due to image quality]

Pregnancy Category B:

[Text illegible]

ADVERSE REACTIONS

1. Malignant hyperthermia
2. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
3. Hypotension and respiratory depression have been reported.
4. Arrhythmias, shivering, nausea, and vomiting have been reported
5. Elevation of the white blood count has been observed

OVERDOSAGE

In the event of overdosage, the following action should be taken:
Stop drug administration; establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:
a) vaporizers calibrated specifically for enflurane;
b) vaporizers from which delivered flows can easily and readily be calculated

[Remaining body text illegible due to image quality]

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ETHRANE (enflurane) is packaged in 125 and 250 ml amber-colored bottles.

Ethrane (enflurane) **10** years of experience confidence safety

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Pharmacokinetics of a single I.V. dose of 6.4 μg/kg fentanyl base in man[1]

ng/ml of Plasma — Hours after injection

Slightly depressed spontaneous respiration below 1.5 ng/ml; normal respiration below 0.7 ng/ml.[1]

*__Note:__ Respiratory depression may last longer than analgesic action and this risk increases with increasing doses.

1. McClain DA and Hug CC, Jr.: Intravenous fentanyl kinetics. *Clin Pharmacol Ther* 28(1): 106-114, 1980.

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Protect from light. Store at room temperature.

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FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY
DESCRIPTION
Each ml. contains:

Fentanyl . . . . .50 mcg. (0.05 mg.) as the citrate
Warning: May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0-7.5.

CONTRAINDICATIONS
SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS
AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.
RESUSCITATION EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.
See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration, and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition. Where moderate or high doses are used (above 10 mcg./kg.), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received SUBLIMAZE (fentanyl). It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Drug Dependence—SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure—SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children—The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy—The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS
The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of SUBLIMAZE (fentanyl) are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol) hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol).

When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS
As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with *INAPSINE* (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION
                                                            50 mcg. = .05 mg. = 1 ml.
Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

I. *Premedication*—Premedication (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly 30 to 60 minutes prior to surgery.

II. *Adjunct to General Anesthesia*—See Dosage Range Chart

III. *Adjunct to Regional Anesthesia*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

IV. *Postoperatively (recovery room)*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usual Children's Dosage: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 20 to 30 mcg. (0.02 to 0.03 mg.)(0.4 to 0.6 ml.) per 20 to 25 pounds is recommended.

DOSAGE RANGE CHART

> **TOTAL DOSAGE**
>
> **Low dose**—2 mcg./kg. (.002 mg./kg.) (.04 ml./kg.) SUBLIMAZE* injection. Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period. *Maintenance:* Additional dosages of SUBLIMAZE* injection are infrequently needed in these minor procedures.
>
> **Moderate dose**—2-20 mcg./kg. (.002-.02 mg./kg.)(.04-0.4 ml./kg.) SUBLIMAZE* injection. Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential. *Maintenance:* 25 to 100 mcg. (0.025 to 0.1 mg.)(0.5 to 2.0 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.
>
> **High dose**—20-50 mcg./kg. (.02-.05 mg./kg.)(0.4-1 ml./kg.) SUBLIMAZE* injection. During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20-50 mcg./kg. (.02-.05 mg.)(0.4-1 ml.) of SUBLIMAZE* injection with nitrous oxide oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH, and prolactin.
>
> When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression.
>
> The main objective of this technique would be to produce "stress free" anesthesia. *Maintenance:* Maintenance dosage (ranging from 25 mcg. (.025 mg.)(0.5 ml.) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

As a General Anesthetic
When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg./kg. (.05 to 0.1 mg./kg.)(1 to 2 ml./kg.) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg./kg. (.15 mg./kg.)(3 ml./kg.) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

OVERDOSAGE
Manifestations: The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; and oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

HOW SUPPLIED
2 ml. and 5 ml. ampoules—packages of 10
NDC 50458-030-02 **NDC** 50458-030-05

10 ml. and 20 ml. ampoules—packages of 5
NDC 50458-030-10 **NDC** 50458-030-20
(For intravenous use by hospital personnel
specifically trained in the use of narcotic analgesics).

March, 1980. Revised June, 1980. January 1981
U.S. Patent No. 3,164,600

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JPI-255

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> 3645 Warrensville Center Rd.
> Cleveland, Ohio 44122, U.S.A.
>
> Telephone: (216) 295-1124

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

57th CONGRESS to be held MARCH 13-17, 1983

THE NEW ORLEANS HILTON AND TOWERS

GENERAL MEETING INFORMATION

SCIENTIFIC PROGRAM:

The deadline for receipt of abstracts of papers for consideration by the Program Committee has passed. Abstracts which were submitted by the August 25, 1982 deadline date will be acknowledged by the Program Committee Chairman: E. Paul Didier, M.D., Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905.

SCIENTIFIC EXHIBITS:

The deadline for submitting scientific exhibit applications is December 31, 1982. Application forms are available from: B. B. Sankey, M.D., International Anesthesia Research Society, 3645 Warrensville Center Rd., Cleveland, Ohio 44122. Tel: (216) 295-1124.

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MEETING REGISTRATION MATERIAL:

Preliminary program, meeting registration and hotel reservation cards will be mailed in December 1982 to all I.A.R.S. members, associate members and educational members. Members residing outside of the U.S. who wish to attend the meeting should advise the I.A.R.S. Cleveland office by Deccember 1 so that registration material can be sent airmail.

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EDITORIAL

A Perspective on Halothane-Induced Hepatotoxicity

INTRODUCED in 1956, halothane rapidly gained wide popularity as a general anesthetic. Reports of severe hepatoxicity in relatively few patients (1-6), however, have curtailed its use. Most of the patients manifesting this disease have high serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) values and massive hepatic necrosis. The necrosis often is centrilobular (2) although other histologic lesions have been reported (1, 5). One of the most striking features of this rare form of disease is that most of the patients have received halothane on previous occasions (2, 3, 6, 7).

In addition to this severe form of hepatoxicity caused by halothane, however, milder forms of hepatic changes are frequently observed after the administration of halothane and other inhalation anesthetics (8, 9). The relationship between these mild disorders and the massive hepatic necrosis that occurs rarely is not clearly understood.

The possibility that metabolic intermediates might cause either the mild or severe forms of toxicity was raised by the discovery that liver microsomes convert halothane to chemically reactive metabolites both anaerobically and aerobically. Under anaerobic conditions, halothane ($CF_3CHClBr$) is reduced by liver microsomes to the reactive metabolite, 1-chloro-2,2,2-trifluoroethyl radical ($CF_3CHCl\cdot$) (10-18). This intermediate is believed to abstract a hydrogen atom from tissue molecules to produce 1-chloro-2,2,2-trifluoroethane (CF_3CH_2Cl) or be reduced by cytochrome P-450 to form 1-chloro-2,2,2-trifluoroethyl carbanion ($(CF_3CHCl:)^{-1}$), which can either eliminate fluoride to produce 1-chloro-2,2-difluoroethylene (CF_2CHCl) or chloride to form trifluoroethyl carbene ($CF_3CH:$). Both the reactive radical and carbene metabolites can react with liver microsomal protein and lipid and presumably other unidentified target substances in liver. In air, however, liver microsomes catalyze oxidation of halothane to a halohydrin intermediate ($CF_3COHClBr$) which spontaneously loses either hydrochloric acid or hydrobromic acid to form an acyl halide (CF_3COX) that either acylates tissue molecules or undergoes hydrolysis to trifluoroacetic acid (13, 14,

19, 20). Both oxidative and the reductive cleavage reactions are catalyzed by the form of liver cytochrome P-450 that is induced by treating rats with phenobarbital.

The finding that a mild form of liver necrosis frequently occurs when rats pretreated with phenobarbital are dosed with halothane and placed in a 14% oxygen atmosphere, but does not occur when the animals are placed in air or are not dosed with halothane or not pretreated with phenobarbital (10-12, 14, 16), thus supported the view that reductive cleavage of halothane could cause liver necrosis. It was felt that patients might experience similar conditions during anesthesia inasmuch as they are exposed to various drugs that induce liver cytochrome P-450 and often might become hypoxic during or following anesthesia with halothane or other inhalation anesthetics (21-23).

Recent papers (23-27), however, have pointed out that hypoxia itself may cause a mild form of hepatic necrosis that is similar to the necrosis observed with halothane in rats and have raised the possibility that much of the hepatoxicity is caused by hypoxia caused by anesthesia rather than by a chemically reactive metabolite of halothane.

Shingu, Eger, and Johnson (26) have shown that high concentrations of halothane administered briefly to phenobarbital-pretreated rats produced more centrilobular necrosis than did low concentrations administered over longer periods of time. As hepatic clearance of halothane is believed to be saturable under these conditions, less total metabolism should have occurred when halothane was most toxic. Moreover, Van Dyke et al (24, 25) have also come to the conclusion that metabolites of halothane may not be responsible for the hepatoxicity observed in rats and humans. Van Dyke (25) has found that enflurane and isoflurane, which are metabolized at considerably less rapid rates than is halothane, also produce centrilobular necrosis in a rat model. He found, however, that enflurane and isoflurane produced liver necrosis only when they were administered for 2 hours at 8% oxygen to rats that had been fasted for 24 hours. If

the rats were not fasted, no toxicity was observed. Fasting also appeared to make the rats more sensitive to the toxic effects of halothane. Van Dyke (25) has suggested that fasting may lead to reduced perfusion of the liver, which in turn may contribute to a decreased oxygen delivery and add to the severity of the hypoxia caused by the inhalation anesthetics and the initial low oxygen tensions. Shingu, Eger, and Johnson (27) have also studied the effects of 24 hours of fasting on hepatotoxicity. In contrast to Van Dyke, they found that when rats were exposed to 8% oxygen for 2 hours, the livers showed signs of damage even without the presence of an inhalation anesthetic. Based on these results, it is possible that enflurane and isoflurane may have had only marginal effects on the hepatotoxicity observed by Van Dyke. If this were the case, then his results would neither support nor exclude the idea that halothane and other inhalation anesthetics cause hepatotoxicity by increasing hypoxia in the liver.

Because of differences in experimental design and differences in the source of the animals, however, it is difficult to resolve the issues between the proponents of the reductive cleavage theory and the proponents of the hypoxia theory. The incidence of halothane-induced hepatotoxicity is highly variable in Sprague-Dawley rats from different sources, and thus the toxicity may not always be reproduced in different laboratories (I. G. Sipes, personal communication, 1982). Different scoring of liver damage has been used; for example, Van Dyke (25) scored toxicity as being either positive or negative, whereas Shingu et al (26, 27), McLain et al (10), Jee et al (12), and Sipes et al (14) used a graded method ranging from 0 (normal) to 5 (extensive necrosis). Moreover, Van Dyke (25) and Shingu et al (26, 27) used oxygen tensions (6% to 10%) considerably lower than the 14% used by proponents of the reductive cleavage mechanism (10–12, 14, 16). It may well be, therefore, that the various groups are evaluating different mechanisms.

It is possible that neither of these mechanisms, which result in a mild form of hepatotoxicity, accounts for fulminant hepatotoxicity observed in humans. Indeed the finding that most victims of this severe form have received halothane on previous occasions suggests a hypersensitivity reaction (2, 3, 6, 7). Although no one has yet shown that patients recovering from halothane-induced hepatotoxicity are sensitized to their own hepatocytes, studies have indicated that this may actually occur.

Sera from patients recovering from severe halothane hepatotoxicity have been shown to contain antibodies that bind to surface membranes of hepatocytes from rabbits treated in vivo with halothane and render them susceptible to cytotoxicity by normal lymphocytes (28). In contrast, sera from normal patients or patients recovering from mild halothane-induced hepatotoxicity did not contain similar antibodies (28, 29). These results suggest that halothane is metabolized to a product that reacts covalently with their external surface of hepatocytes. In susceptible individuals, these altered hepatocyte membranes may be immunogenic and on further exposure to halothane a hypersensitivity reaction may ensure.

Recent investigations (30) have indicated that the metabolite of halothane that interacts with the rabbit hepatocytes to make them susceptible to binding with human antibodies is trifluoroacetyl chloride or bromide (CF_3COX) and not a reductive metabolite product. This conclusion was based on the finding that cytotoxicity was induced by human antibodies against hepatocytes isolated from rabbits anesthetized with halothane at oxygen concentrations of 40% and above but not at lower oxygen tensions that promote reductive metabolism. Indeed, the trifluoroacetyl group has been shown to serve as a hapten when conjugated to human or guinea pig albumin (31).

In conclusion, we believe that halothane-induced hepatotoxicity should be considered as at least two entities. One variety is a mild form of toxicity that is seen commonly after anesthesia with halothane. The animal studies at low oxygen tensions appear to serve as a model for this toxicity since the toxicities produced are usually mild and frequently produced throughout a population of animals. As discussed above, however, carefully controlled investigations are needed to determine whether the toxicity produced under hypoxic conditions is due to either the direct toxic effects of reduction metabolites or to increased hepatic hypoxia produced by halothane. Quite possibly both mechanisms may be important, depending on the initial hypoxic conditions. In any case, this toxicity might be avoided by adequately ventilating patients after surgery (21).

The hypersensitivity theory for the fulminant type of halothane hepatotoxicity is also attractive. It can explain why the disease is rare and is nearly always associated with repeated administrations of halothane. More work is needed, however, before this theory is proven. It will be necessary either to produce the hypersensitivity reaction in animals or to show
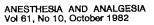
that patients recovering from halothane-induced fulminant necrosis are sensitized to their own hepatocytes.

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Hepatic Centrilobular Necrosis in Rats after Exposure to Halothane, Enflurane, or Isoflurane

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Exposure of phenobarbital-pretreated rats to low concentrations of halothane (0.5%) and reduced oxygen tension (FI_{O_2} 0.08) resulted in the development of liver necrosis in 51% of the animals. Fasting of rats for 24 hours before the same type of exposure increased the incidence of liver necrosis to 80%. Exposure of fed rats to enflurane (1.5%) and isoflurane (1.4%) in conjunction with low oxygen tensions resulted in no liver necrosis; however, in fasting animals, these same concentrations, when accompanied by low oxygen concentrations, produced an incidence of liver necrosis of 35% and 80%, respectively. Lower concentrations of enflurane or isoflurane failed to produce hepatotoxicity. In this study, in addition to increasing the incidence of toxicity, fasting reduced the glutathione levels and also increased cytochrome P-450 concentrations. Exposure to halothane and to isoflurane, but not to enflurane, further decreased the glutathione level. Perhaps the mechanism of liver toxicity associated with anesthesia, at least in this animal model, is related more directly to severe hypoxia than to a direct toxic intermediate produced as a result of metabolism.

Key Words: LIVER: toxicity; TOXICITY: liver; ANESTHETICS, Volatile: halothane, enflurane, isoflurane; METABOLISM: fasting.

ORGAN TOXICITY that occasionally ensues after use of volatile anesthetics has been thought to be caused by the metabolism of these agents. This process has been substantiated in the case of methoxyflurane; its metabolism results in the release of inorganic fluoride, a nephrotoxin. Furthermore, in many instances an increase in metabolism of methoxyflurane has resulted in an increase in the severity of nephrotoxicity (1). Metabolism of halothane has also been suspected of producing organ toxicity; when accompanied by reduced oxygen tensions (2, 3), it has been shown to result in hepatic necrosis in rats. Nevertheless, direct evidence for involvement of a halothane metabolite in this type of toxicity has never been discovered. Therefore, to date, only circumstantial evidence exists to support the role of metabolism in the toxicity of this agent.

Enflurane and isoflurane are metabolized to a much lesser extent than halothane—approximately 20% of halothane (4), 2.4% of enflurane (5), and 0.17% of

isoflurane (6) are metabolized. Although no reactive metabolites have been detected during isoflurane metabolism, enflurane metabolism results in the formation of an acyl chloride that is capable of reacting with and binding to proteins (7). The amount of resultant binding, however, is so minimal that it is unimportant. Furthermore, the limited metabolism of enflurane and isoflurane requires oxygen. In contrast, halothane undergoes metabolism in either the presence or the absence of oxygen, and qualitative differences between the two conditions are apparent.

The metabolism of halothane under reduced oxygen tension is the basis for the rat model of halothane hepatitis (2). Rats in which hepatic microsomal enzymes have been induced by phenobarbital show evidence of centrilobular necrosis 24 hours after 2 hours of exposure to halothane and low concentrations of oxygen (FI_{O_2} 0.08). In our laboratory, the halothane hepatitis model has been studied for several years. The prolonged study was necessary because development of the liver lesion after exposure to halothane and low oxygen concentrations was not always reproducible. Recent studies indicate, however, that another factor may contribute to the development of the lesion. This report describes the effect of fasting on the development of centrilobular necro-

sis in rats after exposure to low concentrations of oxygen and not only halothane but also enflurane and isoflurane.

Methods

Animals and Treatments

Male Sprague-Dawley rats, weighing 250 to 300 g each, were obtained from Hilltop Farms (Scottdale, PA). All rats were given phenobarbital in their drinking water (0.2%) for 5 days and then given untreated water for 24 hours before the experiments. Fed rats were given food ad libitum until immediately before they were used as experimental animals, whereas fasting rats had their food removed 24 hours before the experiments.

The rats were exposed to anesthetic gas mixtures in a Plexiglas chamber with a volume of approximately 50 L. The oxygen concentration within the chamber was continuously monitored by means of a Bio Marine Industries oxygen analyzer. The desired oxygen concentration was achieved by mixing oxygen and nitrogen through calibrated flowmeters. Anesthetic gas vapors were added to the gas mixture by means of a copper kettle. Flow rates through the chamber were maintained at approximately 4 L/min. The concentration of anesthetic used was the same in all experiments: halothane 0.5%, enflurane 1.5%, and isoflurane 1.4%. These were the minimal concentrations required to produce hepatotoxicity. In all of the low-oxygen experiments reported in this study, F_{IO_2} of 0.08 was used.

After a 2-hour exposure, animals killed 2 or 4 hours after exposure were allowed water but no food until being killed, whereas animals killed 24 hours after exposure were given food and water ad libitum. Immediately following killing, liver samples were obtained for fixation and hematoxylin and eosin staining. The histologic slides were screened for liver necrosis with assistance from the Mayo Clinic Department of Anatomic Pathology. The slides were graded only as being positive or negative for centrilobular necrosis, which by definition includes the appearance of dead hepatocytes in the centrilobular region with or without extension into the midzonal area. Thus, diffuse necrosis and ballooning degeneration were graded 1+ and not considered positive in this study, whereas central necrosis graded 2+ or more was considered positive. Liver samples were also removed for microsome preparation and glutathione (GSH) analysis.

GSH Assay

Liver samples were homogenized in three volumes of cold 5% trichloroacetic acid, and hepatic GSH (acid-soluble thiols) was determined in the protein-free supernatant according to the method of Ellman (8).

Microsomal Enzymes

Livers were homogenized in three volumes of 0.15 mM Tris buffer, pH 7.4. The homogenate was centrifuged at 10,000 X g, and microsomal pellets were prepared by centrifuging the 10,000 X g supernatant fraction at 105,000 X g. Hepatic microsomal protein concentration was determined by the method of Lowry (9) and cytochrome P-450 level assayed by the method of Omura and Sato (10). The in vitro metabolism of halothane, the methods used to achieve aerobic and anaerobic incubation conditions, and the determination of inorganic fluoride by the ion-specific fluoride electrode have been described previously (11).

The data in Tables 2 and 3 are presented as means ± SE. Student's t-test was used to determine statistical significance.

Results

Hepatic centrilobular necrosis as a result of exposure to 0.5% halothane and F_{IO_2} of 0.08 was not found in all animals 24 hours later (Table 1). A summary of several experiments indicated that the incidence of necrosis in fed animals exposed to 0.5% halothane was 51%. In contrast, the incidence of necrosis was greater in fasting rats that were exposed to the same conditions. No liver necrosis was seen in fed rats that were exposed to 1.4% isoflurane or 1.5% enflurane in conjunction with an F_{IO_2} of 0.08, but necrosis was seen in animals that had been fasting for 24 hours before

TABLE 1

Incidence of Centrilobular Necrosis in Fed or Fasting Rats Exposed to 8% Oxygen and Anesthetic Agent for 2 Hours 24 Hours before Killing

Anesthetic	Concentra-tion	Study group (no. of rats)	Presence of liver necrosis	
			No.	%
Halothane	0.5%	Fed (92)	46	51
		Fasting (60)	48	80
Enflurane	1.5%	Fed (38)	0	0
		Fasting (60)	21	35
Isoflurane	1.4%	Fed (33)	0	0
		Fasting (60)	48	80

exposure to either anesthetic agent and the same low oxygen tensions. At a concentration of 1.2%, neither enflurane nor isoflurane produced evidence of liver toxicity, a pattern that suggests a sharp dose-response curve. Use of higher concentrations of enflurane and isoflurane (more than 1.5% and 1.4%, respectively) resulted in the death of many animals during exposure, presumably because of respiratory depression.

The characteristic morphologic features in the area

of a central vein in the liver of fasting animals exposed to 8% oxygen only are shown in Fig 1. The central region appeared normal, whereas the periportal areas had small vacuoles that were characteristic of exposure to low oxygen concentrations but that seemed to be more extensive in livers from fasting animals than in livers from those that were fed. In Fig 2 is shown the typical appearance of liver sections from animals that were fasted for 24 hours and then were exposed
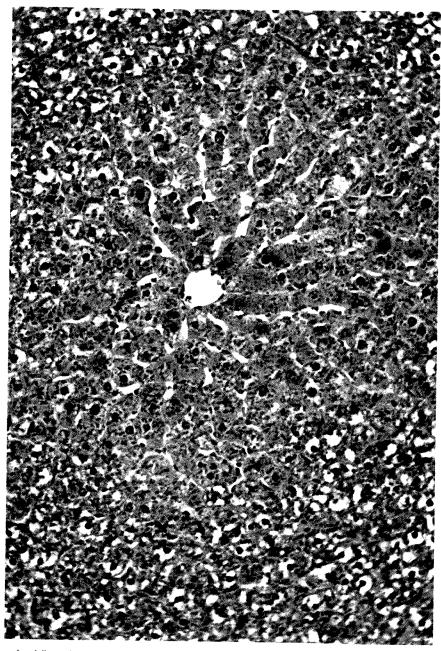
FIG 1. Photomicrograph of liver tissue from fasting rat 24 hours after exposure to low oxygen concentration (F_{IO_2} 0.08) for 2 hours. Hematoxylin and eosin, 160×.

to 0.5% halothane and F_{IO_2} of 0.08; the centrilobular necrosis had extended into the midzone and vacuolization had developed in the periportal area. Liver sections stained for lipids failed to show any evidence of extensive accumulation of fat in the vacuoles in either the central or the periportal region, but some central cells contained an increased amount of extremely small lipid droplets.

The characteristic morphologic features of liver specimens obtained from fasting animals exposed to 1.5% enflurane and F_{IO_2} of 0.08 are shown in Fig 3; the centrilobular necrosis had extended into the midzone. The central necrosis that is typically found in fasting animals exposed to 1.4% isoflurane and F_{IO_2} of 0.08 is depicted in Fig 4. The tissue from neither enflurane- nor isoflurane-exposed animals showed any large accumulation of fat. The cells in the central region showed ballooning degeneration and some dead cells were also present.

The cytochrome P-450 measurements are shown in Table 2; there is a statistically significant increase in cytochrome P-450 levels in fasting animals as compared with fed animals. There was also a statistically significant increase in the anaerobic release of inorganic fluoride from halothane in the microsomes from the fasting as compared with the fed animals, which merely reflected the difference in cytochrome P-450 content.

GSH levels in livers from rats exposed to halothane, enflurane, or isoflurane and low concentrations of oxygen are shown in Table 3. Fasting decreased GSH levels, which were further decreased immediately after exposure to halothane but which rebounded to levels greater than those found before exposure. Animals exposed to enflurane showed no change in GSH levels at the three times after exposure, whereas isoflurane exposure resulted in a rebound effect similar to that found after exposure to halothane. Exposure
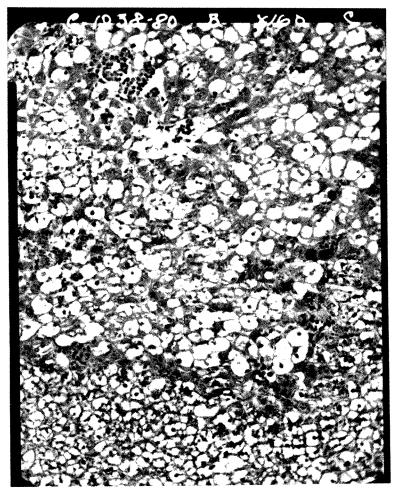
Fig 2. Photomicrograph of liver tissue from fasting rat 24 hours after exposure to 0.5% halothane and low oxygen concentration (F_{IO_2} 0.08) for 2 hours. Note extensive vacuolization and necrosis in central and midzonal areas. Hematoxylin and eosin, 160×.
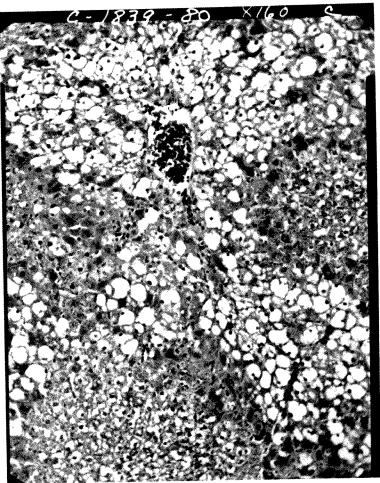
Fig 3. Centrilobular and midzonal necrosis in liver from fasting rat 24 hours after exposure to low oxygen concentration (F_{IO_2} 0.08) and 1.5% enflurane for 2 hours. Hematoxylin and eosin, 160×.

to low oxygen concentrations (F_{IO_2} 0.08) alone for 2 hours had no effect on the GSH levels.

Discussion

The mechanism of development of hepatic necrosis by xenobiotics has never been established. Of particular concern in this regard is the hepatitis occasionally noted in humans after subjection to halothane anesthesia and that seen in the rat model after exposure to halothane and low inspired oxygen concentrations. Because the rat model of halothane hepatitis seems to be related to the metabolism of the agent under reduced oxygen tensions, the mechanism of development of hepatic necrosis has been presumed to be the result of the generation of reactive intermediates in the course of metabolism. No toxic metabolites, however, have been identified. Thus, the relationship of metabolism to toxicity is only circumstantial, and because of the nature of the data in this report, it is

appropriate to consider another mechanism that involves severe hypoxia not necessarily related to metabolism.

As reported herein, centrilobular necrosis can be induced by enflurane and isoflurane, which do not undergo a substantial degree of metabolism (5, 6). This finding raises the possibility that physiologic factors may play a role in the development of hepatic necrosis, which in turn suggests that centrilobular necrosis as an end point in toxicity studies may be subject to three interpretations: (a) the mechanism of development of necrosis may be so varied that no single factor can be implicated—that is, the end point is not related to a specific cause; (b) the metabolites of xenobiotics thought to interact chemically with sensitive sites in the cell may instead react with receptors to produce physiologic changes, such as reduced or altered organ perfusion, that result in decreased oxygen delivery; or (c) metabolism of xeno-
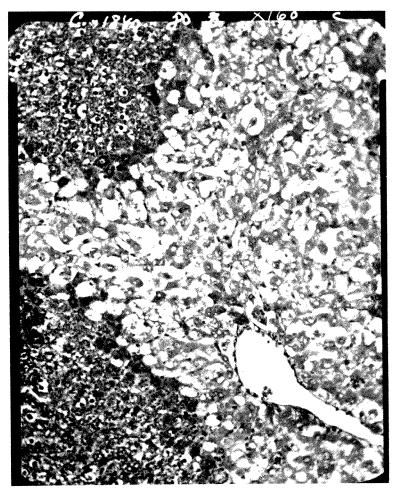
FIG 4. Centrilobular necrosis and vacuolization in liver from fasting rat 24 hours after exposure to 1.4% isoflurane and low oxygen concentration (F_{IO_2} 0.08) for 2 hours. Hematoxylin and eosin, 160×.

TABLE 2

Cytochrome P-450 Levels and Inorganic Fluoride Generated from Halothane in Microsomes from Fed and Fasting Rats*

Study group	Cytochrome P-450	Inorganic fluoride
	nmol/mg protein	μmol/mg protein
Fed	1.85 ± 0.06	4.39 ± 0.39
Fasting	2.40 ± 0.04	6.15 ± 0.54
p	<0.001	<0.05

* Values are means ± SE.

biotics plays no role but because of the apparent correlation with toxicity obscures the physiologic effects of the parent compound.

Halothane metabolism under reduced oxygen tensions leads to the formation of metabolites that covalently bind to cellular constituents (12). Under normal oxygen tensions there is some binding of a halothane metabolite to protein; however, when the oxygen tension is reduced, the covalent binding increases but the increase is completely attributable to binding with fatty acids in phospholipids (13). Exposure of rats to low oxygen tensions in the presence of halothane produces centrilobular necrosis. This apparent relationship among low oxygen concentration, binding, and toxicity has been the basis for implicating metabolism in the mechanism of toxicity. Pretreatment with phenobarbital or polychlorinated biphenyls (PCBs) is also necessary for the production of hepatotoxicity; this factor has further implicated the role of metabolism because cytochrome P-450, which is induced by this treatment, mediates the metabolism of halothane. The present study also seems to support this implication because fasting, which enhances toxicity, also causes an increase in cytochrome P-450 (Table 2).

Studies in this laboratory and others, however, have shown that measurable cytochrome P-450 content decreases under the same conditions as those that

TABLE 3

Glutathione Levels in Fasting Rats: Effect of Exposure to Anesthetic Agent and 8% Oxygen or to 8% Oxygen Alone*

	Glutathione		
	Immediately	At 2 hours	At 4 hours
	μmol/g liver		
After exposure to:			
Halothane	3.27 ± 0.39†	4.57 ± 0.08‡	5.20 ± 0.22‡§
Enflurane	3.81 ± 0.14†	3.93 ± 0.10†	4.09 ± 0.14†
Isoflurane	3.59 ± 0.13†	4.62 ± 0.24‡	4.64 ± 0.20‡§
Low O₂	4.63 ± 0.67†	3.25 ± 0.32†	3.71 ± 0.25†

* Values are means ± SE. Glutathione levels (μmol/g liver) in nonexposed control rats were: fed, 6.14 ± 0.06; fasting, 3.98 ± 0.15.

† Not significantly different from fasting control rats.

‡ Significantly different ($p < 0.005$) from fasting control rats.

§ Significantly different ($p < 0.01$) from immediately after exposure.

promote the hepatotoxicity—namely, halothane plus low oxygen tensions (13, 14). The reduction in measurable cytochrome P-450 has been reported to be as high as 70%, is found immediately after exposure, and persists for at least 24 hours. In addition, the enzymatic activity also decreases in parallel with the measurable content. Thus, the induction of cytochrome P-450 may not be the most important change but only one of many changes produced in the liver as a result of phenobarbital or polychlorinated biphenyl treatment. The key alteration is still not known but may be related to the oxygen requirement and perfusion patterns in the liver.

Enflurane and isoflurane do not undergo metabolism to a considerable extent and, as stated previously, no reactive metabolites have been detected under reduced oxygen tensions. Yet both anesthetics produce liver toxicity in fasting animals exposed to low oxygen concentrations during anesthesia. A key question now is: do enflurane and isoflurane depress either the respiratory or the circulatory system and thus cause severe liver hypoxia, and, if so, might halothane also do the same? Normally, the liver has a limited oxygen content (15); therefore, exposure to an anesthetic may readily reduce its oxygen content to hypoxic levels. Halothane is known to reduce hepatic blood flow in humans (16). Whether enflurane or isoflurane produces the same effect is not known; however, both enflurane and isoflurane are respiratory depressants, and in our experiments in which the animals breathed spontaneously the hypoxemia associated with respiratory depression would have become apparent.

Neither enflurane nor isoflurane has any effect on cytochrome P-450 levels, and because these agents are metabolized to a limited extent, the destruction of

P-450 by halothane can be assumed to result from formation of reactive metabolites. Chemicals that are metabolized by way of a reactive intermediate have been noted to cause an initial reduction of GSH often followed by an increase above control levels. This rebound effect on levels of GSH has been attributed to the stimulation of GSH synthesis by reactive intermediates (17) and is consistent with the observation that the rate of GSH synthesis can be stimulated above that normally found when the demand increases. The present study shows not only the previously reported effect of fasting on GSH levels, but also the rebound effect—that is, GSH levels were greater 4 hours after than immediately after exposure to halothane and low oxygen concentrations (Table 3). Investigators have previously reported (18) that GSH levels remain unchanged after administration of halothane. In that study, however, oxygen tensions were too high to produce liver toxicity or to increase reactive intermediates to a level necessary to affect the rate of GSH synthesis. Moreover, the determinations were made at times after exposure when changes in GSH levels would not have been evident. Nonetheless, isoflurane seems to have the same effect as halothane on reduced GSH levels. Both agents cause a rebound of reduced GSH levels after exposure, which has been assumed to be the result of formation of reactive metabolites; this sequence of events suggests that reactive metabolites may not be the only determinants of reduced GSH levels.

The effect of fasting is not clear. Perhaps the perfusion of the liver by the portal system is reduced after fasting, and this reduction contributes to a decreased oxygen delivery and adds to the hypoxia caused by hypoxemia secondary to respiratory depression. A recent report (19) indicates that centrilob-

ular injury can be detected in isolated perfused livers as a result of hypoxia produced by reducing the delivery of oxygen to the liver. The proposal that centrilobular necrosis induced by halothane, enflurane, or isoflurane in the rat model is the result of severe hypoxia is open to many questions; nevertheless, the hypothesis is in accordance with currently reported data.

ACKNOWLEDGMENTS

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Hypoxia Per Se Can Produce Hepatic Damage without Death in Rats

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SHINGU, K., EGER, E. I., II, AND JOHNSON, B. H.: Hypoxia per se can produce hepatic damage without death in rats. Anesth Analg 1982;61:820-3.

To evaluate the importance of hypoxia itself on halothane-induced hepatic injury in the rat, the question of whether hypoxia could injure the liver without causing death was investigated. Male Sprague-Dawley rats pretreated with phenobarbital (1 mg/ml of drinking water, 4 days) and deprived of food for 24 hours were exposed to 6%, 7%, 8%, or 10% inspired oxygen with 0%, 5%, or 7.5% carbon dioxide for 2 hours. Several rats died when given 6% oxygen with 0% or 7.5% carbon dioxide, but all other rats survived. Without carbon dioxide, oxygen at a concentration of 7% or 8% produced more injury than did room air, and 6% oxygen produced the most severe damage. These results demonstrate that in rats hypoxia per se may be an important factor in causing hepatic damage.

Key Words: HYPOXIA: liver; LIVER: hypoxia.

IN RATS PRETREATED with phenobarbital to enhance drug metabolism, exposure to halothane and low (but not high) concentrations of oxygen produces hepatic injury (1, 2). Furthermore, in vitro (3-5) and in vivo (6) binding of halothane metabolites to rat liver microsomal lipids increases at lower concentrations of oxygen. These results support the hypothesis that intermediate(s) of the reductive biodegradation of halothane may be hepatotoxic. However, recent studies (7) suggest that this interpretation of the above experiments may underestimate the importance of hypoxia itself as a cause of hepatotoxicity. That is, although reductive metabolism occurs, it may not be the real cause of injury.

In rats pretreated with phenobarbital and then deprived of food for 24 hours before exposure to an anesthetic in a hypoxic environment, halothane, enflurane, and isoflurane all caused hepatic injury (7). As enflurane and isoflurane are minimally metabolized (8), this suggests that not only might lack of food contribute to hepatic injury but also that metabolism of anesthetics may not be necessary for pro-

duction of hepatic damage by anesthetics. Because these three anesthetics depress respiration and circulation, they might cause hepatic injury by compromising hepatic oxygenation.

It is obvious that some level of liver hypoxia must produce injury. What is less obvious is whether this level is compatible with survival. That is, one cannot assume that hepatic injury produced in vitro would apply in vivo. In fact, there is little experimental evidence indicating that hypoxia can produce in vivo hepatic injury. Refsum (9) reported that plasma serum glutamine oxaloacetic transaminase (SGOT) levels increased in patients with pulmonary insufficiency when arterial oxygen content decreased to less than 9 ml/dl. Iles et al (10) showed that blood levels of succinate derived from the liver increase in patients in whom Pa_{O_2} values were less than 50 to 60 torr. In both of these clinical studies, factors other than the level of oxygen may have played a role in the hepatic injury that occurred. To evaluate the importance of hepatic oxygenation, we studied whether hypoxia with or without carbon dioxide could cause hepatic injury in the absence of anesthesia.

Methods

One hundred eight male Sprague-Dawley (Charles River) rats weighing approximately 250 g each, were given phenobarbital (1 mg/ml of drinking water) for 4 days (mean 21.5 ± 0.3 (SE) mg/day). For the next

24 hours they drank pure water and were deprived of food. The rats than were assigned to groups according to the concentration of oxygen and carbon dioxide in the inspired gas. The control group (n = 12) breathed room air. The "10% oxygen" group (n = 9) breathed 10% oxygen plus 7.5% carbon dioxide. The remaining animals breathed 8% (n = 26), 7% (n = 25), or 6% (n = 36) oxygen. Each of these three groups was divided into three subgroups according to the amount of carbon dioxide added, i.e., 0%, 5%, or 7.5%. The animals were placed in individual Plexiglas tubes (6.5 cm i.d. and 30 cm length), and they were exposed to the mixture of oxygen and carbon dioxide (balance nitrogen) for 2 hours. The flow through each tube was approximately 1 L/min. Every 5 to 10 minutes, inflow concentrations of oxygen and carbon dioxide were checked with a Beckman model E2 oxygen analyzer and a Beckman LB2 medical gas analyzer, respectively. After exposure, the rats were returned to individual cages and were given rat chow and water ad libitum. After 24 hours the rats were killed by exposure to carbon dioxide, and sections of the right superior hepatic lobe were taken for microscopic examination. Each section was fixed and stained with hematoxylin and eosin. The resulting slides were arranged in a random sequence and hepatic injury was scored "blindly" by a pathologist. Each liver was assigned a score of 0 (normal) to 5 (extensive cell disruption with multiple necrosis over 25% of field area) according to the criteria of Jee et al. (11). The statistical significance of differences between groups was tested using the Mann-Whitney U-test (12).

Results

During exposure to 6% oxygen without carbon dioxide, nine of 18 rats died. Convulsions preceded all deaths, and some survivors also convulsed. Although addition of 5% or 7.5% carbon dioxide prevented convulsions, six of nine rats died when given 7.5% carbon dioxide with 6% oxygen. All other animals survived.

When it occurred, hepatic injury was characterized by centrilobular necrosis and vacuolization. The normal lobular architecture was maintained, but cells in the centrilobular regions showed pyknotic nuclei, loss of nuclei, large vacuoles, and loss of cell margins. Cells in periportal areas appeared to be spared from injury.

Livers from two control rats were assigned a score of 3 (mean 1.67 ± 0.27 [SE]) (Table), suggesting that pretreatment with phenobarbital followed by 24 hours of food deprivation can itself cause hepatic injury. The addition of carbon dioxide seemed to have a favorable effect; without carbon dioxide, oxygen at concentrations of 7% or 8% produced more injury than that found in livers of control rats ($p < 0.01$). However, livers of rats given 7% and 8% oxygen and 5% or 7.5% carbon dioxide did not differ from livers of control rats (except those given 7% O_2 + 5% CO_2). At the same oxygen concentration, there were no significant differences among groups that had received carbon dioxide and those that had not. Livers from rats given 6% oxygen showed significantly more damage than livers from rats given 7%, 8%, or 10%

TABLE

Effects of Hypoxia and Carbon Dioxide on Hepatic Injury*

CO₂	O₂				Room air
	6%	7%	8%	10%	
0%	4.56 ± 0.36‖ (9/18)	3.50 ± 0.45§ (8/8)	3.12 ± 0.32‡ (8/8)		1.67 ± 0.27 (12/12)
5%	4.70 ± 0.22‖ (10/10)	2.63 ± 0.28† (8/8)	1.89 ± 0.37 NS (9/9)		
7.5%	5.00 ± 0.00‡ (3/9)	2.22 ± 0.49 NS (9/9)	2.22 ± 0.42 NS (9/9)	2.78 ± 0.16‡ (9/9)	

* Values are means ± SEM using values criteria of Jee et al (11). A score of 0 = normal liver, 5 = multiple area necrosis. Values in parentheses indicate the number of rats survived/studied. Comparison to the room-air group was made by Mann-Whitney U-test. NS, Not significant.
† $p < 0.05$.
‡ $p < 0.01$.
§ $p < 0.005$.
‖ $p < 0.001$.

oxygen, regardless of whether or not carbon dioxide was concomitantly administered ($p < 0.02$) (except 6% O_2 + 0% CO_2 vs 7% O_2 + 0% CO_2).

Discussion

Our results show that hypoxia can cause hepatic injury in the absence of anesthesia. They suggest that the liver may be more vulnerable to hypoxia than the brain or heart. The results support (but do not prove) the suggestion of Van Dyke (13) that anesthetics may cause hepatic injury by depressing ventilation and/or decreasing hepatic blood flow.

Carbon dioxide was added to the inspired gases in some groups to mimic more closely hypoxia induced by hypoventilation. We considered that the addition of carbon dioxide might have had several effects on hepatic oxygenation in our preparation. First, it would further stimulate breathing and thereby decrease hypoxemia. Second, it would shift the oxyhemoglobin dissociation curve to the right and thereby decrease arterial oxygen content. And third, it might directly cause hepatic vasodilation and increase hepatic blood flow (and oxygen delivery), or indirectly (through sympathetic stimulation) cause vasoconstriction and decrease flow. The results with 7% and 8% oxygen suggested that the addition of carbon dioxide exerted a favorable effect. The lack of an effect with 6% oxygen may simply reflect the profound impact of this low level of oxygen. The effect of carbon dioxide in protecting against hypoxia agrees with the results of Brauer (14) who found the secretion rate of bile in rats does not decrease with hypoxia (F_{IO_2} of 0.05 to 0.1) if 5% carbon dioxide is added to the inspired gas mixture. Furthermore, Cooperman et al (15) reported that hypocapnia increased the oxygen demand of splanchnic viscera out of proportion to the associated increase in blood flow in paralyzed humans anesthetized with nitrous oxide.

Our histologic findings indicative of centrilobular injury are similar to those reported to be induced by halothane in animals (1, 2, 11) and humans (16, 17). The region around the central vein is the last site to receive oxygen and nutrients in the liver lobulus. It therefore has the lowest oxygen tension and might be most influenced by hypoxia. Although decreased perfusion to liver causes centrilobular anoxia, normoxia persists in the periportal region in the isolated perfused rat liver (18). In this preparation, structural derangements appear to be confined to the centrilobular region. Centrilobular injury also may be caused by ethanol (19), hyperthyroidism, narcotics (20), and

anesthetics. Ethanol and hyperthyroidism increase hepatic oxygen consumption (19). Narcotics and anesthetics depress respiration and circulation. All these effects could result in centrilobular hypoxia; perhaps this is the common mechanism by which hepatic injury results from such diverse causes.

Why does pretreatment with phenobarbital predispose the liver to injury in the model we used? Phenobarbital induces microsomal enzymes and increases the metabolism of various drugs. The fact that hepatic injury from exposure to halothane appears to require pretreatment with phenobarbital has been thought to indicate the importance of anesthetic metabolism to hepatic damage. However, phenobarbital influences more than the quantitative or qualitative (21) hepatic metabolism of drugs. It increases the amount of microsomal protein (3) by decreasing the rate of breakdown and by enhancing the rate of synthesis (22). Does phenobarbital also increase oxygen demand, and is this demand further augmented by the metabolism of anesthetics? Does phenobarbital augment the ongoing processes of cellular breakdown and repair and thereby increase oxygen consumption?

Why does food deprivation make the liver more vulnerable to injury or itself cause injury? The fact that livers from two rats in the control group received scores of 3 suggests that lack of food produces serious hepatic effects. Goldschmidt et al (23) reported that a high-carbohydrate diet protects against hepatic damage induced by chloroform and divinyl ether. Food deprivation might influence the liver in several ways. It decreases the availability of substrates for metabolism and for synthesis of cell constituents; it changes the activities of various enzymes (24); and it decreases hepatic blood flow. Regardless of the underlying mechanism, the effects of food deprivation may have important clinical implications. Surgical patients are always deprived of food for several hours before operation; also, some patients undergo surgery in malnourished states.

We conclude that although the reductive biodegradation of halothane may play some role in hepatic injury, its role might not be as important as previously believed. Hypoxia itself may be a more important factor than formerly appreciated. If so, all anesthetics, both injected and inhaled, may prove to be hepatotoxic by virtue of their effects of ventilation, hepatic blood flow, or the distribution of hepatic blood flow.

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Hypoxia May Be More Important than Reductive Metabolism in Halothane-Induced Hepatic Injury

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SHINGU, K., EGER, E. I., II, AND JOHNSON, B. H.: Hypoxia may be more important than reductive metabolism in halothane-induced hepatic injury. Anesth Analg 1982;61:824-7.

To evaluate the relative importance of halothane metabolism and liver hypoxia in the occurrence of hepatic injury, the injury produced in hypoxic rats exposed to identical MAC hours of halothane but at various concentrations of halothane was compared. Groups of male Sprague-Dawley rats were pretreated with phenobarbital for 4 days, and 24 hours later they were exposed to 10 hours of 10% oxygen and concomitantly 0.2 MAC hours of halothane at the following anesthetic concentrations: 0.02% for 10 hours, 0.1% for 2 hours, 0.5% for 24 minutes, or 2.5% for 4.8 minutes. A control group received only 10% oxygen for 10 hours. Liver specimens taken 24 hours later demonstrated concentration-dependent damage; high concentrations given briefly produced more damage than lower concentrations given for long periods. As hepatic clearance of halothane by metabolism appears to be a saturable phenomenon, these results suggest that hypoxia per se may be more important than halothane metabolism in causing liver damage.

Key Words: ANESTHETICS, Volatile: halothane; BIOTRANSFORMATION: halothane; TOXICITY: halothane; HYPOXIA: liver; LIVER: hypoxia, halothane.

IT HAS BEEN suggested that the intermediate products of halothane biodegradation in animals breathing oxygen at a low partial pressure may play a major role in halothane-induced hepatic injury. Rats pretreated with phenobarbital to enhance drug metabolism develop hepatic injury following exposure to halothane at low (but not high) concentrations of oxygen (1, 2). Lower concentrations of oxygen increase binding of halothane metabolites to rat liver macromolecules (3, 4).

The thesis that reductive metabolism is primarily responsible for hepatic injury may not be correct: hypoxia per se may be as or more important. Van Dyke (5) reported that isoflurane and enflurane, which are metabolized in small amounts, also produce hepatic damage in starved hypoxic rats pretreated with phenobarbital. We found that nonlethal hypoxia in the absence of any anesthetic can produce liver injury (6).

We devised an experiment to test the relative importance of metabolism versus hypoxia, based on the following assumptions. Hepatic clearance of halothane by metabolism (i.e., the fraction of halothane in the blood flowing through the liver that is removed by metabolism) is greatest at trace halothane concentrations (i.e., 0.001%). Both published and unpublished data suggest that half saturation (i.e., the K_m) of metabolism occurs at approximately 0.0003 atm (0.03%) of halothane (7). Higher concentrations cannot more than double metabolism (i.e., approach V_{max}, the maximum rate of metabolism). Thus, administering a low concentration of halothane for a prolonged period should produce more metabolites (and, if reductive metabolism is important, more injury) than a short exposure at a high concentration. This prediction has been shown to be true for enflurane and methoxyflurane (8). On the other hand, although higher concentrations of anesthetic given for a short time might produce less metabolites, they may produce more hepatic hypoxia and hepatic injury as a consequence of cardiorespiratory depression. The following experiment tested these predictions: that the occurrence of more injury after a long exposure of anesthetic at a low concentration would indicate the

importance of reductive metabolism, whereas the occurrence of more injury after a short exposure at a high concentration would point to the importance of hepatic hypoxia.
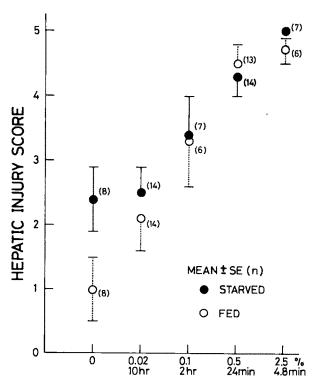
Methods

Male Sprague-Dawley rats, weighing 371 ± 5 g (mean ± SE) each were housed individually in metal mesh cages and were given 0.1% phenobarbital in their drinking water for 4 days (mean 29.9 ± 0.6 (SE) mg/day). For the next 24 hours, half the rats were given pure water but were deprived of food. The other half were given pure water and rat chow. A control group of rats (eight had received food and eight had not) then were exposed to 10% oxygen (nitrogen balance) for 10 hours. The remaining groups of rats also breathed 10% oxygen for 10 hours and, concomitantly, halothane at various concentrations. All were exposed to the same total dose of halothane (the concentration times the duration of exposure) at the midpoints of the 10-hour period of hypoxia. The mean concentrations of halothane and the lengths of exposure were as follows: 0.021% ± 0.005% (SD) for 10 hours (n = 28), 0.100% ± 0.007% for 2 hours (n = 14), 0.526% ± 0.006% for 24 minutes (n = 28), or 2.45% ± 0.008% for 4.8 minutes (n = 14). Half the rats in each group had been starved for 24 hours before exposure and half had not. All animals were placed individually in Plexiglas tubes, and they were deprived of food and water during the 10-hour exposure. The flow rate through each tube was approximately 1 L/min. Halothane was delivered from a Fluotec MK2 and was diluted to the desired concentration by addition of oxygen and nitrogen. During the exposure to halothane, gas samples from the delivery tube were taken every 1 to 15 minutes (the frequency of sampling was dependent on the duration of anesthetic exposure), and the concentrations of halothane were measured with gas chromatography. The inflow concentration of oxygen was checked every 5 to 15 minutes with a Beckman model E2 oxygen analyzer. After exposure, the rats were given rat chow and water ad libitum. Twenty-four hours later, the rats were killed with 100% carbon dioxide, and sections of the right superior hepatic lobe were taken for microscopic examination. Each section was fixed and stained with hematoxylin and eosin. The resulting slides were arranged in a random sequence and hepatic injury was scored "blindly" by a pathologist. Each liver was given a score of 0 to 5 using the criteria of Jee et al (9), that is, 0 = normal; 1 = mild

cellular disruption (some dissociation of centrilobular hepatic cords), <25% of field area; 2 = moderate cell disruption, appearance of balloon cells and vacuolizations, <50% of field area; 3 = extensive cell disruption and vacuolization, >50% of field area; 4 = extensive cell disruption with occasional centrilobular necrosis; and 5 = extensive cell disruption with multiple centrilobular necrosis, >25% of field area. Statistically significant differences between groups were tested using the Mann-Whitney U-test (10).

Results

Three rats died while breathing 10% oxygen: one each in the 0.1%, 0.5%, and 2.5% halothane groups. These rats had been fed in the 24-hour period before breathing low concentrations of oxygen. The histologic scores were clearly related to the concentration of halothane rather than the length of exposure (Figure). The longest exposure to halothane (0.02%) produced no more liver damage than that found in the control groups. In contrast, rats exposed to 0.5% or 2.5% halothane had the most severe hepatic injury (p

FIGURE. Relationship of hepatic injury score to concentration of halothane and length of exposure.

< 0.005, compared with the control group), despite the brevity of exposure. Exposure to 0.1% halothane produced more injury than exposure to hypoxia alone in fed rats (p < 0.02), but not in starved rats. A statistical difference between the scores of starved and fed rats appeared only in the control group (p < 0.05). The only other significant difference appeared in a comparison of starved rats given 0.1% versus 2.5% halothane (p < 0.01).

Discussion

Several reports suggest that the value of K_m (the concentration at which half-saturation of enzymes occurs) for halothane metabolism is well below that required for anesthesia: 0.03% in humans (7), 0.007% in rats (11), and 0.04% in swine (12). Although these values describe metabolism at normal oxygen concentrations (i.e., oxidative metabolism), it has been reported that the cytochrome P-450 system mediates both oxidative metabolism and reductive metabolism. The kinetics of reductive metabolism of halothane have not been determined directly. However, Gandolfi et al (13) reported K_m values of 0.11 to 0.22 mM for the covalent binding of metabolites of radioactive halothane to microsomal protein and lipid when incubated under nitrogen in vitro. Assuming a solution/gas partition coefficient of 1, 0.11 to 0.22 mM converts to 0.28% to 0.56% halothane. As these figures apparently were based on the volumes of halothane injected rather than on direct measurements of halothane concentration, losses of halothane vapor could cause a significant overestimate of the K_m, which in any case is in the subanesthetic range.

If the reductive metabolism of halothane saturates at a trace or subanesthetic concentration, the amount of metabolites should be proportional to the dose of halothane at lower concentration, and should be proportional to exposure time at higher concentrations. Once the K_m is significantly exceeded, further increases in the concentration of a substance that is toxic by virtue of its metabolism should not further increase toxicity. The case of 1,1-dichloroethylene shows this plateau in toxicity by saturation of metabolism (14). The mortality of rats is proportional to the concentration of 1,1-dichloroethylene inhaled between 100 and 200 ppm, but shows a plateau at greater than 200 ppm (0.02%).

This evidence suggests that if the intermediates of reductive metabolism of halothane play a major role in causing hepatic damage, the severity of such damage in our model should have been greater at the

lower concentrations than at the higher concentrations. However, that was not the case. On the other hand, the degree of liver hypoxia may be directly related to the concentration (but not dose) of halothane. Higher halothane concentrations might produce liver hypoxia by hypoventilation, or by depression of hepatic blood flow, or by an adverse redistribution of flow (e.g., an increase in portal flow at the expense of hepatic artery flow). Thus, our results suggest that liver hypoxia per se may be a more important factor than metabolism of halothane in causing hepatic damage.

However, it should be noted that there is an alternative explanation for our results which would still sustain the hypothesis that reductive halothane metabolism is important to hepatic injury. Because the reductive metabolism of halothane is inhibited by oxygen (15), the rate of this process may have been increased by the more severe hypoxia produced by the higher concentrations of halothane in our study.

We deprived half of our rats of food for 24 hours before exposure to hypoxia because Van Dyke's results (5) suggested that starvation increases the vulnerability of the liver to injury. Starvation depletes liver tissue of glutathione (16), which acts as an antidote against various hepatotoxic chemicals (15). However, two reports (1, 17) suggest that reductive intermediates of halothane do not conjugate to glutathione. Only in our control group did starved rats show significantly more damage than fed rats. Perhaps this result indicates that starvation makes liver tissue more vulnerable to hypoxia, but that this effect is masked by addition of halothane.

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Intravenous Nitroglycerin and Myocardial Metabolism during Anesthesia in Patients Undergoing Myocardial Revascularization

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SETHNA, D. H., MOFFITT, E. A., BUSSELL, J. A., RAYMOND, M. J., MATLOFF, J. M., AND GRAY, R. J.: Intravenous nitroglycerin and myocardial metabolism during anesthesia in patients undergoing myocardial revascularization. Anesth Analg 1982;61:828–33.

Although intravenous nitroglycerin has been used to control the hypertensive response during sternotomy in patients undergoing myocardial revascularization, the effects of the drug on myocardial oxygen supply and demand have not been described in this clinical setting. Eight adult patients with good ventricular function (ejection fraction >50%), who were anesthetized for coronary artery bypass, were studied before and after administration of intravenous nitroglycerin (mean dose 12 μg/kg in 6 minutes). Evaluation of myocardial metabolism showed an increase in coronary sinus oxygen content ($p < 0.05$) and a reduction in myocardial oxygen consumption ($p < 0.05$). Although mean myocardial lactate extraction and coronary sinus blood flow were not significantly altered in the group as a whole, variations in individual patient responses were observed and are discussed. These direct observations of global myocardial metabolism observed in this study group are similar to the conclusions reached by other investigators using indirect indices of myocardial oxygen supply and demand.

Key Words: SURGERY: cardiovascular; ANESTHESIA: cardiovascular; ANESTHETIC TECHNIQUES: hypotensive, nitroglycerin.

G LYCERYL TRINITRATE (nitroglycerin) has been the drug of choice for relieving myocardial ischemia for more than 100 years (1). Recently, nitroglycerin administered intramuscularly (2) and intravenously (3) has been used during anesthesia to control hypertension and avoid myocardial ischemia before (3), during (4–8), and after surgery (9) in patients undergoing myocardial revascularization. The sys-

temic hemodynamic effects of intravenous nitroglycerin have been described in detail in such a setting. In the varying doses (up to 96 μg/min) used in these studies, the drug caused a consistent dose-dependent decrease in systemic and pulmonary arterial, pulmonary capillary wedge, and right atrial pressures (3, 4, 6–8). Although indirect indices of myocardial oxygenation indicate a decrease in myocardial oxygen demand when intravenous nitroglycerin is used to control intraoperative hypertensive responses in patients undergoing surgery for myocardial revascularization (7, 8), the associated myocardial metabolic effects of the drug have not been reported. The goal of the present study was to examine the effects of intravenous nitroglycerin on the coronary circulation and myocardial metabolism in patients anesthetized for myocardial revascularization when the drug is used to control the hypertensive response to sternotomy.

Methods and Materials

After informed consent was obtained, eight male patients (mean age, 56 ± 8 (SD) years) were studied

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according to a protocol approved by our Human Subjects Committee. All patients had significant coronary arterial disease (>50% diameter narrowing, range of diseased vessels, 1 to 3), and were scheduled for elective coronary artery bypass grafting within 4 weeks of diagnostic cardiac catheterization. Although five patients had remote myocardial infarctions, all had good ventricular function with ejection fractions greater than 0.52 at the time of catheterization. All patients had normal sinus rhythm. Excluded from our study were patients with diabetes mellitus, valvular heart disease, arterial hypertension (diastolic blood pressure > 105 mm Hg), significant pulmonary disease, left ventricular end-diastolic pressure (LVEDP) >20 mm Hg at rest or >15 mm Hg after nitroglycerin, and patients with myocardial infarction within 2 weeks of surgery. Patients with angiographically minimal (trace) mitral regurgitation were included. Patients 1 and 5 (Table 1) were taking propranolol and patients 5, 6, and 7 were being treated with long-acting nitrates. All medications were continued until the night before surgery. Premedication consisted of secobarbital, 100 mg, orally the night before surgery, and 3.0 mg/kg orally 1 hour before going to the operating room. In addition, five patients had intravenous propranolol (mean dose 7.8 mg) 1 hour before anesthesia.

In the operating room the following catheters were inserted: (a) an 18-gauge cannula into the radial artery;

(b) a thermodilution triple-lumen catheter (Edwards Laboratories, Santa Ana, CA) into the pulmonary artery via the right internal jugular vein, using the Seldinger technique; and (c) a thermodilution coronary sinus catheter (Wilton-Webster Laboratories, Altadena, CA) through the same internal jugular vein into the coronary sinus by fluoroscopy so that the external thermistor was 10 to 20 mm inside the coronary sinus.

Patients 4 and 7 were anesthetized with morphine (1 mg/kg) and oxygen, and the rest with halothane in oxygen. Induction of anesthesia with halothane began with up to 2.5% halothane inspired in oxygen, and thereafter anesthesia was maintained with 0.5% to 1.0% halothane in oxygen. Ventilation was controlled mechanically. Control measurements were performed after the sternum was incised. A nitroglycerin infusion was then started and rapidly titrated to maintain mean arterial pressure less than 90 mm Hg. The dose of nitroglycerin infused and the time of infusion for each patient are listed in Table 1. No other drugs were administered and intravenous fluids other than those given with the nitroglycerin infusion were not given during the study period. The infusion contained 100 μg/ml of nitroglycerin and was prepared in a standard fashion in our hospital pharmacy (4).

Coronary blood flow was measured by the thermodilution technique as described by Ganz et al (10). Arterial and coronary sinus blood samples were ob-

TABLE 1

Hemodynamic Responses to Intravenous Nitroglycerin after Sternotomy in Patients Undergoing Myocardial Revascularization*

Patient no.	NTG dose	Infusion time	Interven-tion	HR	MAP	PA	SVR	PCW	RA	CI	SVI	SWI
	$\mu g/kg/min$	min		beats/min	mm Hg		$dyne \cdot sec \cdot cm^{-5}$	mmHg		$L/min/m^2$	$ml/beat/m^2$	$g \cdot m/m^2$
1	1.1	7	Before	93	122	33	2850	31	8	1.52	16	26
			After	85	83	18	947	16	7	3.06	36	42
2	2.4	5	Before	55	99	17	1724	17	10	2.47	45	72
			After	51	58	12	1010	11	7	2.42	47	44
3	1.5	6	Before	119	105	34	1823	24	15	1.67	14	19
			After	109	64	12	542	14	7	3.55	33	31
4	1.3	5	Before	65	122	17	2909	16	10	1.60	25	50
			After	71	68	8	1112	8	7	2.28	32	32
5	1.5	5	Before	55	79	17	880	18	10	3.13	57	70
			After	49	55	13	656	15	10	2.74	56	45
6	1.3	8	Before	61	96	30	1600	27	11	2.28	37	57
			After	65	86	17	1313	15	9	2.52	39	51
7	5.2	6	Before	62	126	16	2169	17	8	2.00	32	62
			After	62	91	17	2018	10	6	1.55	25	36
8	2.6	5	Before	64	100	24	1496	20	10	2.46	38	59
			After	64	68	12	1122	7	6	2.25	35	39
Mean ± SD	2.1 = 1.4	6 ± 1	Before	72 ± 23	106 ± 16	24 ± 8	1931 ± 688	21 ± 5	10 ± 2	2.14 ± 0.55	33 ± 15	52 ± 20
			After	70 ± 20	72 ± 13	14 ± 3	1090 ± 452	12 ± 3	7 ± 1	2.55 ± 0.59	38 ± 10	40 ± 7
				NS	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	NS	NS	NS

* Abbreviations used are: NTG, nitroglycerin; HR, heart rate; MAP, systemic mean arterial pressure; PA, mean pulmonary arterial pressure; SVR, systemic vascular resistance; PCW, mean pulmonary capillary wedge pressure; RA, mean right atrial pressure; CI, cardiac index; SVI, stroke volume index; SWI, stroke work index; NS, not significant.

tained simultaneously for measurement of lactate and oxygen concentrations. Lactate was measured in duplicate by modification of the Marbach method (11). Blood samples were analyzed immediately for hemoglobin and oxygen saturation (IL Co-Oximeter model 282). Systemic and pulmonary arterial, pulmonary capillary wedge, and right atrial pressures were measured and recorded on paper using a six-channel chart recorder (VR-6 Electronics for Medicine). Cardiac output was measured by thermodilution. Arterial blood pressure, the electrocardiogram, and the patient's clinical condition were continually monitored. Measurements were repeated after the blood pressure had become stabilized during the nitroglycerin infusion (mean time, 6 ± 1 minutes).

Hemodynamic indices were calculated from measured variables according to standard formulas (12). Metabolic indices were calculated as follows: lactate extraction ratio

$$= \frac{ART \ (lactate) - CS \ (lactate)}{ART \ (lactate)}$$

where ART (lactate) is the arterial lactate concentration (meq/L) and CS (lactate) is the coronary sinus lactate concentration (meq/L).

$$MV_{O_2} = CBF \times [ART \ (oxygen) - CS \ (oxygen)]$$

where MV_{O_2} is oxygen consumption of the myocardium drained by the coronary sinus (predominantly the left ventricular myocardium) and CBF is coronary sinus blood flow.

Statistical evaluation was done by using the Wilcoxon paired test comparing measurements before and after administration of nitroglycerin in each patient (13). Results are expressed as means ± SD. A p value of less than 0.05 was considered statistically significant.

Results

Hemodynamic data before and after the nitroglycerin infusion for each patient are shown in Table 1. In each patient, nitroglycerin decreased calculated systemic vascular resistance (mean 44%, $p < 0.05$). This was accompanied by a decrease in the mean arterial pressure in each patient, with a 32% decrease for the entire group ($p < 0.05$). The reduction in afterload was accompanied by a decrease in preload in each patient, as reflected by decreases in pulmonary capillary wedge pressure (mean 43%, $p < 0.05$) and

right atrial pressure (mean 30%, $p < 0.05$). Mean pulmonary arterial pressure decreased in seven patients and for the group (mean 42%, $p < 0.05$). Although modest variations were observed in responses of individual patients, there were no significant alterations in the heart rate, cardiac index, stroke volume index, and stroke work index for the group.

Patients 4 and 7, who had morphine anesthesia, had the highest mean arterial pressures (122 and 126 mm Hg) before nitroglycerin, and patient 7 required 5.2 μg/kg/min of nitroglycerin to control the blood pressure response to sternotomy. In contrast, the mean control blood pressure for patients receiving halothane anesthesia was 100 mm Hg. In patients 2 and 5, both given halothane anesthesia, the decrease in blood pressure after nitroglycerin was excessive, with mean arterial pressures reaching 58 and 55 mm Hg, respectively, and with small reductions in cardiac index.

Myocardial metabolic findings for each patient are shown in Table 2. An increase in coronary sinus oxygen content was observed in six patients, with a 22% increase in mean coronary sinus oxygen content for the group ($p < 0.05$). This resulted in a reduction in myocardial oxygen consumption in each patient, with a 36% decrease for the group ($p < 0.05$). In patient 2, an adequate blood sample could not be withdrawn from the coronary sinus catheter during the control measurements.

Although no statistically significant changes were seen in the mean coronary hemodynamics for the group, variations in the individual patient responses were present. Coronary blood flow decreased in five patients, especially when coronary perfusion pressure (mean arterial pressure) decreased. Despite this reduction in myocardial oxygen supply, coronary sinus oxygen content was consistently increased suggesting a significant actual overall reduction in myocardial oxygen needs with nitroglycerin.

Although as a group the mean myocardial lactate extraction increased by 33%, individual patient responses were variable, with lactate extraction increasing in four patients and decreasing in two patients. In patient 3 lactate production before administration of nitroglycerin reverted to lactate extraction after drug administration. Lactate extraction probably decreased in patient 2, although no sample was obtainable before the drug was administered.

Continued electrocardiogram monitoring revealed no alterations in cardiac rhythm, ST segments, or T waves.

TABLE 2

Myocardial Metabolic Responses to Intravenous Nitroglycerin after Sternotomy in Patients Undergoing Myocardial Revascularization*

Patient no.	Intervention	CBF	CVR	CS-O_2	MV_{O_2}	MLE	RPP
		ml/min	mm Hg/ml/min	ml O_2/dl	ml/min	%	
1	Before	78	1.46	5.5	8.6	30	14,973
	After	59	1.29	6.0	5.5	40	9,350
2	Before	84	1.06	—	—	—	8,250
	After	38	1.34	6.9	2.1	−37	4,539
3	Before	188	0.48	6.1	22.9	−7	16,065
	After	188	0.30	9.3	14.1	34	10,028
4	Before	76	1.47	7.9	7.0	7	11,765
	After	27	2.26	7.8	2.4	14	6,177
5	Before	84	0.82	4.0	8.2	21	6,600
	After	58	0.78	4.7	4.6	16	4,018
6	Before	148	0.57	6.1	13.6	37	9,821
	After	174	0.44	8.5	11.5	38	7,865
7	Before	66	1.79	8.3	7.1	31	10,726
	After	69	1.23	10.7	5.0	18	7,874
8	Before	91	0.99	6.2	7.9	33	9,536
	After	60	1.03	6.7	5.2	42	6,272
Mean ± SD	Before	102 ± 43	1.08 ± 0.46	6.3 ± 1.4	10.8 ± 5.8	21.7 ± 16	10,967 ± 3,219
	After	84 ± 61	1.08 ± 0.61	7.7 ± 2.0	6.9 ± 4.2	28.9 ± 12	7,015 ± 2,150
		NS	NS	$p < 0.05$	$p < 0.05$	NS	$p < 0.05$

* Abbreviations used are: CBF, coronary blood flow; CVR, coronary vascular resistance; CS-O_2, oxygen content in coronary sinus blood; MV_{O_2}, myocardial oxygen consumption; MLE, myocardial lactate extraction; RPP, rate-pressure product; NS, not significant.

Discussion

Intravenous nitroglycerin can be used in patients with coronary artery disease undergoing myocardial revascularization to control hypertensive responses during intubation and sternotomy (4–8). The clinical usefulness of the drug in this setting must be viewed in the context of both its hemodynamic effects and myocardial metabolic cost. This study examined the myocardial metabolic cost, specifically, the change in myocardial oxygen supply and demand.

It is important to describe the patients studied in accurate detail, because the results obtained in one clinical or hemodynamic setting may not apply to all patients. All our patients had chronic stable angina or medically responsive unstable angina with significant coronary disease. Although five of our patients gave a history of one or more previous documented myocardial infarctions, myocardial function, as evaluated by ejection fraction, was well preserved.

The mean dose of intravenous nitroglycerin used in this study was 2.1 μg/kg/min infused over 6 minutes. It is our clinical experience that large doses are often required to control intraoperative hypertension. Similar to findings of previous studies, the drug caused a significant reduction in arterial and pulmonary blood pressure with a concomitant decrease in

right atrial and pulmonary capillary wedge pressures (3–9). Although Kaplan and Jones (8) observed an increase in the heart rate with nitroglycerin at a dose of 96 μg/min, this effect was not seen in our patients. The increase in cardiac index that would have occurred with the reduction in afterload in our patients was most likely offset by the simultaneous significant reduction in preload, resulting in no observed alterations in the cardiac index.

With regard to myocardial metabolism, nitroglycerin decreased myocardial oxygen needs, as shown by a significant increase in coronary sinus oxygen content without a change in arterial content. This appears as a reduction in the calculated myocardial oxygen consumption. A similar conclusion was reached by Kaplan and Jones (8) using rate-pressure product, triple index, and tension time index as indirect indices of myocardial oxygen consumption. In addition, the study by Hempelmann et al (7) in patients receiving a 2-mg/h nitroglycerin infusion during sternotomy, indicated a reduction in myocardial oxygen demand, using different indirect indices for calculation of myocardial oxygen consumption.

The modest reduction in mean coronary blood flow observed in our patients was most likely related to a reduction in the coronary perfusion pressure (mean

arterial pressure) and is in agreement with the observation of Kaplan and Jones (8), who suggested a reduction in coronary blood flow using the coronary perfusion pressure (diastolic blood pressure minus pulmonary capillary wedge pressure) as an index of myocardial oxygen supply.

Another measure of myocardial oxygenation involves lactate metabolism. Under aerobic conditions, more than 20% of arterial lactate is extracted by the myocardium and used for adenosine triphosphate formation (14). Myocardial lactate production indicates anaerobic metabolism resulting from hypoxia or anoxia. Although myocardial lactate extraction of less than 10% has been cited as an indicator of ischemia, this concept has recently been questioned (15). In our patients, although no significant alteration in the mean myocardial lactate extraction was observed, individual variations were noted as described above.

The limitations of the technique used for measuring coronary sinus blood flow in this study have been summarized elsewhere (16, 17). We feel that this technique provides meaningful data regarding the magnitude and direction of changes in coronary blood flow when measured sequentially in the same patient. A potential technical criticism of the validity of coronary sinus blood flow determination by the thermodilution technique is present when right atrial pressure is elevated (18). In all of our patients, the positional stability of the catheter in the coronary sinus and the absence of major reflux into the mouth of the coronary sinus were assessed as suggested by Mathey et al (18).

On the basis of our data, certain cautions must be kept in mind when interpreting the effects of nitroglycerin on myocardial metabolism in patients with coronary artery disease. Alterations in regional myocardial blood flow, collateral blood flow, and regional myocardial metabolism, particularly in areas of coronary obstruction, may not be reflected in the overall global evaluation of myocardial metabolic function. Such a phenomenon may have occurred in patients 5 and 7, who showed a reduction in myocardial lactate extraction with an increase in coronary sinus oxygen content.

It is essential to note some of the individual patient responses described above to appreciate the potential of the effect of nitroglycerin during anesthesia in patients with coronary artery disease. The drug does control the hypertensive response to sternotomy in anesthetized patients, and, in fact, can produce relief of ischemia as manifested by a reversal of lactate production to extraction. On the other hand, an excessive hypotensive response can occur with a reduction in coronary perfusion pressure and reductions in coronary blood flow and lactate extraction.

In summary, we have documented the cardiovascular effects of intravenous nitroglycerin during anesthesia in patients with obstructive coronary artery disease undergoing myocardial revascularization. The systemic hemodynamic effects observed are similar to those previously described. As concerns global myocardial metabolism, we found an increase in coronary sinus oxygen content. These direct observations on global myocardial metabolism for the group are similar to the conclusions reached by other investigators using indirect indices of myocardial oxygen supply and demand.

ACKNOWLEDGMENTS

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Onset and Progression of Intravenous Regional Anesthesia with Dilute Lidocaine

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Intravenous regional anesthesia was induced in seven healthy volunteers using dilute lidocaine solution. Onset and progression were documented by sequential detailed neurologic examinations and compared with changes following intravenous regional administration of normal saline. On average, lidocaine produced sensory loss earliest on the radial forearm and in the first dorsal web space, although the sequence of development of analgesia was variable, e.g., fingertip analgesia could occur before or after forearm sensory loss. Motor paralysis could precede or follow sensory loss in tissues supplied by the same peripheral nerve; the only consistent finding was persistence of strength in the flexor digitorum profundus of the little finger. The pattern of development of intravenous regional anesthesia was related to the anatomic distribution of the peripheral nerves; it is hypothesized that the primary mechanism of action is block of the small distal nerve branches.

Key Words: ANESTHETIC TECHNIQUES, Regional: intravenous.

A LTHOUGH introduced in 1908 and the subject of considerable investigation since, the mechanism of action and even the pattern of development of intravenous regional anesthesia remain controversial. Reported development of early fingertip analgesia contrasts with a noted persistence of sensation in distal parts. The effects of ischemia may further complicate evaluation (1). The aim of this study was to detail the neurologic progression of intravenous regional block with the view of defining where and how it produces its effect. Dilute lidocaine solution produced slow onset which allowed sequential examination.

Methods and Materials

Seven healthy volunteers (two nonpregnant women and five men; age, 27 to 45 years) were subjected to intravenous regional block of the nondominant arm using a standard technique (2). A plastic intravenous cannula was placed in an ulnar dorsal hand vein, and a tourniquet was applied to the upper arm. Exsan-

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guination with an Esmarch bandage preceded tourniquet inflation to 250 torr for 20 minutes.

Analgesia was induced by injecting a dilute solution of lidocaine (0.25%, 40 ml) without preservative into the bloodless extremity. These experiments served as controls in a study on the effects of intravenous regional reserpine and guanethidine. For this reason injections were repeated with 1 mg of reserpine added to 40 ml of 0.25% lidocaine. Five volunteers underwent block with both solutions, lidocaine and lidocaine with reserpine; one subject received only lidocaine and another one received only lidocaine with reserpine. Two volunteers also received 40 ml of normal saline, and again 1 mg of reserpine in 40 ml of normal saline, substituted for the local anesthetic. A total of 16 experiments were documented. The protocol was approved by the hospital human experimentation committee. Informed consent was obtained from all subjects.

The following examinations were performed at 5-minute intervals after injection and again 10 minutes after tourniquet release: surface sensation was assessed with pin scratch (safety pin), cold (ice cube), and light touch (brush). Only presence or absence of these modalities was recorded. Six skin areas were chosen for their representation of smaller branches of peripheral nerves (Fig 1): radial forearm, musculocutaneous nerve; dorsal first web space, superficial

FIG 1. Schematic drawing of nerves to forearm and hand. Shading denotes skin area chosen for sensory examination.

branch of radial nerve; index finger tip, digital branch of median nerve; thenar eminence, palmar cutaneous branch of median nerve; little fingertip, digital branch of ulnar nerve; and hypothenar eminence, palmar cutaneous branch of ulnar nerve. Position sense was assessed both by discrete motion of the distal interphalangeal joint of the index finger and by motion of the wrist. Vibratory sense was tested with a tuning fork (128 Hz) on the distal radial condyle of the middle phalanx of the index finger and on the ulnar and radial styloid processes.

Motor function was evaluated in five muscles, again chosen for their innervation by different branches of peripheral nerves (Fig 2): flexor pollicis longus, proximal median nerve; opponens pollicis, distal median nerve; first dorsal interosseous, distal ulnar nerve; little finger flexor digitorum profundus, proximal ulnar nerve; and extensor carpi radialis brevis/longus, radial nerve.

Motor function was graded and recorded on a 0 to 5 scale (5, normal; 4, ability to move against resistance; 3, ability to overcome gravity only; 2, ability to move with but not against gravity; 1, trace or palpable contraction; 0, no contraction) (3).

Sympathetic integrity was assessed with psychogalvanic skin reflex. This was recorded on a single channel electrocardiograph machine (Hewlett-Packard, model 1512A) with the electrodes of lead II

MOTOR
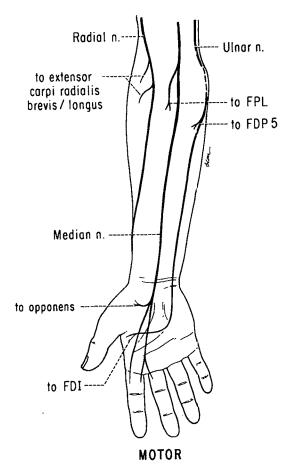
FIG 2. Schematic drawing of nerves to forearm and hand indicating motor branches to muscles tested. Abbreviations used are: FPL, flexor pollicis longus; FDI, first dorsal interosseus; FDP5, little finger flexor digitorum profundus.

connected to the dorsal and palmar surfaces of the hand. The reflex was elicited by electrical stimulation (30 Hz) applied to the left leg, adjusted to produce an unpleasant but not painful paresthesia.

Results

Results from the four experiments using saline alone, and with 1 mg of reserpine added to saline, were indistinguishable. During tourniquet inflation, surface and position sensation were fully preserved when tested after 5 and 10 minutes. Vibratory sense was unaltered at 5 minutes; it was absent 10 minutes following tourniquet inflation except for one instance in which it remained present at the ulnar and radial styloids. Motor power remained unaffected at 5 minutes; it decreased minimally to an average of 4.7 after 10 minutes of tourniquet inflation. Psychogalvanic skin reflex was present at the 5- and 10-minute examinations.

After 15 minutes of tourniquet inflation, changes in surface sensation occurred. They were more pronounced at 20 minutes, but complete surface sensory block was never realized. Position sense disappeared at the 20-minute examination. Motor power decreased to an average of 2 at 20 minutes.

No difference was observed between the examinations after lidocaine alone and after lidocaine with reserpine; they will be noted together. Only data for the 5- and ten-minute examinations following tourniquet inflation will be reported; 15- and 20-minute values were discarded. The neurologic deficits seen at these intervals could not be differentiated from the effects produced by tourniquet and/or saline. In general, analgesia continued to increase to the 20-minute interval, with three subjects attaining surgical anesthesia.

Sensory data are summarized in Table 1; reported values are averages of the lidocaine and lidocaine/reserpine experiments in all subjects (12 observations). On average, surface sensation decreased earliest in the radial forearm and to a lesser extent at the first dorsal web space. In some individuals sensation was not decreased equally in different branches of the same nerve, e.g., proximal areas (thenar and hypothenar) were anesthetic, whereas distal parts (index and little fingertips) remained sensitive, or vice versa. Touch was less affected than was ability to detect cold, pin scratch, and vibration, but followed the same pattern of progression. Position sense was preserved, except for two observations at 10 minutes.

Decrease in motor function was highly variable between subjects, but consistent in the same subject from one experiment to another. The only discernible pattern was persistence of muscle strength in the flexor digitorum profundus of the little finger even beyond the 10-minute examination. The average decrease of strength of each muscle group at the 5- and 10-minute intervals is reported in Table 2 (12 obser-

TABLE 2

Average Motor Strength following Intravenous Regional Block with 0.25% Lidocaine*

Muscle	5 min	10 min
FPL	2.2	1.6
Opponens	3.9	2.8
FDI	3.3	3.0
FDP 5	4.2	3.7
Wrist extensor	3.0	1.9

* Abbreviations used are: FPL, flexor pollicis longus; FDI, first dorsal interosseus; FDP 5, little finger flexor digitorum profundus.

vations in seven subjects). Psychogalvanic skin reflex decreased throughout the experiment; it was absent in four subjects at 5 minutes, and in six at 10 minutes.

Ten minutes after release of tourniquet, all sensory and motor function had returned to preexperimental values in all experiments.

Discussion

Onset and progression of intravenous regional anesthesia have shown considerable variation in previous reports. A pattern of early analgesia in the fingertips with subsequent proximal spread has been observed (4, 5). Contrarily, persistence of sensation in the fingertips in the presence of forearm and hand analgesia has also been noted (6). Neurologic deficit from ischemia alone may be difficult to separate from the effect of the local anesthetic (1, 7, 8).

In this study, the results when saline alone was injected indicate that ischemia per se produced minimal neurologic deficits consisting of slight decrease of motor power and absent vibration sense during the first 10 minutes of observation. Thus, changes in surface sensation during the first 10 minutes of anesthesia reflected the effect of local anesthetic only. These changes could be discretely evaluated with the dilute lidocaine solution with its slow onset and progression of analgesia.

TABLE 1

Average Examinations of Surface Sensation following Intravenous Regional Block with 0.25% Lidocaine*

Skin area	5 min			10 min		
	Pin	Cold	Touch	Pin	Cold	Touch
Forearm radial	83% (10)	92% (11)	25% (3)	100% (12)	100% (12)	50% (6)
1st web space	58% (7)	75% (9)	8% (1)	75% (9)	92% (11)	25% (3)
Fingertip 2	25% (3)	25% (3)	0% (0)	42% (5)	42% (5)	17% (2)
Thenar	8% (1)	17% (2)	0% (0)	33% (4)	33% (4)	17% (2)
Fingertip 5	16% (2)	42% (5)	8% (1)	42% (5)	58% (7)	33% (4)
Hypothenar	25% (3)	42% (5)	8% (1)	66% (8)	58% (7)	25% (3)

* Percentage refers to the average loss of this modality; values in parentheses denote the number of subjects showing loss.

Early analgesia was found in a strip along the dorsal radial aspect of the forearm and hand, areas innervated by the musculocutaneous and superficial radial nerves, respectively. In individual subjects, however, the sequence of development of analgesia was random; fingertip analgesia could precede or follow forearm sensory loss. Patterns were consistent, however, on repeat examination in the same subject. Position sense was only minimally affected, reflecting the low concentration of drug. Vibratory sense was diminished earlier when lidocaine was injected than when saline was used; however, the effects of tourniquet inflation could not be separated from those produced by lidocaine. On motor examination the only pattern was persistence of good strength in the flexor digitorum profundus of the little finger.

Sensory loss followed the sequence of classic differential block, with cold and pin sensations being affected before touch. Position sense was always affected last. Motor loss could precede or follow sensory loss in tissues supplied by the same peripheral nerve. Early loss of motor function agrees with the results of recent animal experiments showing that larger fast-conducting nerve fibers (e.g., motor) are more sensitive to local anesthetics than smaller slow-conducting fibers (e.g., pain and some sensation) (9). Thus, motor block may appear before onset of analgesia. Alternatively, intravenous regional anesthesia may act primarily on the small motor or sensory branches of peripheral nerves. As smaller nerves are more readily affected by dilute concentrations of local anesthetics and are of pure motor or sensory function, it is as likely that a motor branch would be blocked as a sensory branch. The order of sequence of blockade would depend on the distribution of drug through the venous system. This explanation is supported by our observation that the sequence in which neurologic changes developed in the distribution of any one sensory branch followed the classic pattern of sensitivity of sensory nerves to local anesthetics.

The mechanism of action of intravenous regional anesthesia has remained controversial (1). Present evidence favors the production of nerve block anesthesia, and radiographic contrast studies have suggested nerves in the elbow region to be the most likely target (4). However, this does not explain the speed of onset and short recovery time (1, 10). In addition, the persistence of sensation in areas with insufficient circulation is not compatible with this hypothesis (6, 11).

These discrepancies are resolved by the concept that the primary site of action of local anesthetics is on small peripheral nerve branches. This is illustrated in our study by the occurrence of analgesia in one branch of a specific nerve with persistence of sensation in another branch of the same nerve. Primary action on the distal nerve branches still agrees with the findings supporting the hypothesis that intravenous regional anesthesia is produced by multiple peripheral nerve blocks, but it satisfies the objections. Rapid onset may be explained by the greater susceptibility of small nerves to local anesthetics. Low concentrations used in regional block are diluted even further when spreading through the ischemic limb. The small amount of drug fixed by small peripheral nerves is adequate to produce axonal blockade because of the large surface area in smaller distal branches, but may be rapidly removed when circulation is restored. This would explain the rapid recovery after tourniquet release. Reports showing absence of analgesia with poor circulation are based on observations of fingertips. This study showed distal analgesia to be highly variable from subject to subject. Short observation periods or pooling of smaller volumes of anesthetic may account for persistent fingertip sensation.

The occurrence of distal analgesia when local anesthetic is injected between two tourniquets remains to be explained (4, 12). In experiments demonstrating this phenomenon, large volumes or high concentrations of drug were injected into a relatively small space. The resulting concentrations of local anesthetics were marginal for the production of conventional peripheral nerve block, but the relatively large exposed surface area of nervous tissue between the two tourniquets allowed delayed onset of distal block. The amount of drug absorbed into nerve fibers remained insufficient, however, to sustain anesthesia after circulation was restored, resulting in rapid recovery. The rapid onset of analgesia between tourniquets further supports the concept of small nerve block as the primary mechanism of anesthesia of intravenous regional anesthesia.

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Prophylactic Intravenous Ephedrine Infusion during Spinal Anesthesia for Cesarean Section

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KANG, Y. G., ABOULEISH, E., AND CARITIS, S.: Prophylactic intravenous ephedrine infusion during spinal anesthesia for cesarean section. Anesth Analg 1982;61:839-42.

Ephedrine sulfate was administered to 44 healthy parturients undergoing elective repeat cesarean section under spinal anesthesia. Twenty patients received ephedrine infusion (0.01% solution, beginning with approximately 5 mg/min) immediately after induction of spinal anesthesia to maintain maternal systolic blood pressure between 90% and 100% of the base line systolic blood pressure (mean dose of ephedrine 31.6 mg). Twenty-four patients (control group) received 20 mg of ephedrine as an intravenous bolus, and additional 10-mg increments, if necessary, when systolic blood pressure decreased to 80% of the base line systolic blood pressure (mean dose of ephedrine 26.8 mg). In patients given the infusion, systolic blood pressure did not change significantly from the base line systolic blood pressure following spinal anesthesia ($p > 0.1$) and reactive hypertension did not occur. Nausea and/or vomiting occurred in nine women in the control group and one patient in the infusion group ($p < 0.001$). Apgar scores, fetal blood gas tensions, and time for onset of respiration were comparable in the two groups. The results suggest that prophylactic ephedrine infusion is safe and desirable in healthy parturients undergoing cesarean section under spinal anesthesia.

Key Words: ANESTHETIC TECHNIQUES: spinal; ANESTHESIA: obstetric.

IN SPITE of left uterine displacement and prehydration, hypotension occurs in 50% to 80% of patients undergoing cesarean section under spinal anesthesia (1-3). Maternal hypotension may decrease uterine blood flow causing fetal hypoxia, acidosis, and neonatal depression (4). Additional measures have been suggested to prevent or treat maternal hypotension following spinal anesthesia. Shnider and associates (5) recommend that hypotension be treated by intravenous injections of ephedrine, whereas Gutsche (6) suggests that ephedrine be given intramuscularly before induction of spinal anesthesia. Mathru and associates (7) have reported that prehydration with 5% albumin (15 mg/kg) prevented maternal hypotension during spinal anesthesia. Clark and Brunner (8) treated maternal hypotension following spinal anesthesia with an intravenous infusion of

dopamine but found that dopamine was not superior to ephedrine.

The techniques mentioned above were helpful in maintaining maternal blood pressure but there are potential disadvantages inherent in each of these techniques. The continuous intravenous infusion of ephedrine titrated against maternal blood pressure during spinal anesthesia in obstetrics has been suggested (9) but has not been adequately investigated.

The purpose of this study was to determine whether prophylactic intravenous infusion of ephedrine can effectively maintain maternal blood pressure without adversely affecting the mother or fetus.

Methods and Materials

This study was approved by the Research, Review and Human Experimentation Committee of Magee-Womens Hospital and informed consent was obtained from each patient. Forty-four healthy parturients scheduled for elective, repeat cesarean section were randomly assigned to one of two groups (continuous infusion or bolus injection of ephedrine). Patients arrived at a holding area 1 hour before induction of anesthesia. Maternal arterial blood pressure and heart rate were monitored at 10-minute

intervals with the patient in the left lateral position using a vital signs monitor (Dinamap model 845, Critikon). The means of the recorded values were regarded as the base line systolic blood pressure (BSBP) and heart rate. Each patient received an intravenous infusion of lactated Ringer's solution, 15 ml/ kg, within 20 minutes before induction of spinal anesthesia. With the patient in the left lateral position, tetracaine, 0.5% in 5% dextrose, was injected. The patient was then turned to the supine position with a 15 degree wedge under the right hip for left uterine displacement. Oxygen, 6 L/min, was administered via a disposable plastic mask. Ephedrine (50 mg in 500 ml of lactated Ringer's solution) was piggybacked on the intravenous line using a 16-gauge needle and the infusion started in 20 patients immediately after the intrathecal injection of tetracaine. The infusion was administered at the rate of approximately 5 mg of ephedrine per minute (50 ml/min) for the initial 2 minutes following the induction; thereafter, the rate of infusion was manually adjusted to maintain systolic blood pressure (SBP) between 90% and 100% of the BSBP. Once SBP was stabilized, the ephedrine infusion was discontinued and the intravenous line was "kept open" with lactated Ringer's solution. If hypotension persisted despite the maximum infusion rate of the ephedrine, 10 mg of ephedrine was given intravenously as a bolus. Twenty-four patients (control group) received 20 mg of ephedrine as an intravenous bolus when SBP decreased to 80% of BSBP. When necessary, additional 10-mg boluses of ephedrine were administered to maintain SBP greater than 80% of BSBP. Thereafter, patients in both groups received lactated Ringer's solution according to their requirements.

From the time of induction to delivery, SBP, diastolic blood pressure, mean blood pressure, and heart rate were monitored and automatically recorded at 1-minute intervals, or more frequently when indicated, using a Dinamap monitor and electrocardiogram. Immediately after delivery, maternal arterial and umbilical arterial and venous blood samples were obtained from a maternal radial artery and a clamped segment of the umbilical cord. Measurements of pH, P_{CO_2}, and P_{O_2} were performed using a Corning model 168 blood gas analyzer and base deficit was calculated from the Siggaard-Andersen nomogram. The times of induction of anesthesia, start of surgery, uterine incision, and delivery were recorded.

A pediatrician, who was unaware of the group assignment, determined the 1- and 5-minute Apgar scores and time for onset of sustained rhythmic res-

piration. Parturients were instructed to report any unusual changes; thus nausea and vomiting were recorded as subjective complaints from patients. Proportional data were compared by chi-square analysis. Analysis of variance and the Newman-Keuls multiple range test were used to compare changes in blood pressure and heart rate. A p value of 0.05 was considered statistically significant.

Results

The characteristics of the patients are shown in Table 1. There were no statistically significant differences between the two groups in maternal age, gravidity, maternal weight, neonatal weight, gestational age, base line blood pressure, level of sensory block, tetracaine dosage, prehydration volume, total hydration volume up to delivery time, ephedrine dosage, induction-to-delivery time, and uterine-incision-to-delivery time. In the control group, five patients (21%) maintained SBP above 80% of the BSBP without vasopressor. In the remaining 19 patients in the control group, systolic hypotension was treated with bolus injections of ephedrine. Two patients given infusions of ephedrine required a 10-mg bolus of ephedrine in addition to the ephedrine drip infusion to maintain SBP above 90% of the BSBP. Changes in SBP in the two groups are shown in the Figure. In patients given the infusion of ephedrine, SBP did not change signif-

TABLE 1

Characteristics of Two Groups of Patients*

	Infusion group (n = 20)	Bolus injection group (n = 24)
Maternal		
Age (yrs)	29.8 ± 4.2	29.9 ± 3.1
Gravidity	2.50 ± 0.9	2.25 ± 0.7
Weight (kg)	78.0 ± 12.6	73.3 ± 10.0
Base line SBP (torr)	124.8 ± 7.9	122.0 ± 6.8
Level of anesthesia (T)	4.1 ± 1.0	4.2 ± 0.9
Tetracaine dosage (mg)	7.8 ± 0.7	7.9 ± 0.6
Prehydration (ml/kg)	14.3 ± 1.9	15.4 ± 2.1
Hydration prior to delivery (ml/kg)	22.6 ± 2.4	24.4 ± 2.2
Ephedrine dosage (mg)	31.6 ± 8.8	26.8 ± 9.8
Induction-to-delivery time (min)	16.0 ± 4.9	15.5 ± 3.8
Uterine incision-to-delivery time (sec)	70.5 ± 23.7	78.3 ± 30.6
Fetal		
Weight (g)	3428 ± 324	3419 ± 421
Gestational age (wk)	39.0 ± 0.7	39.3 ± 0.8

* Values are means ± SD. There were no statistically significant differences between the two groups.
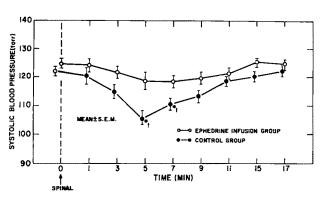
FIGURE. Systolic blood pressures with prophylactic ephedrine infusion (O———O) and with therapeutic bolus ephedrine injection (●———●). * Significantly different from base line value ($p < 0.001$). † Significantly different from corresponding value during infusion of ephedrine ($p < 0.025$).

icantly from preanesthetic levels. In the control patients, SBP was significantly lower 5 and 7 minutes after induction of anesthesia. In the control group, systolic hypotension was most severe 5 minutes after induction of spinal anesthesia and SBP did not return to base line levels until approximately 6 minutes later in spite of aggressive treatment. Three patients in the control group (13%) experienced SBP greater than the base line values (13%, 15%, and 9% increase) compared with one patient in the infusion group (3%) ($p = 0.1$). The maximal increase in maternal heart rate was similar in both groups, from 93 to 113 ± 13 beats per minute during the infusion of ephedrine and from 96 to 119 ± 17 beats per minute in the control group. With infusion of ephedrine, all patients maintained SBP above 70% of the BSBP, whereas, in the control group, in three patients (13%) SBP was less than 70% of BSBP ($p = 0.1$).

Nausea and vomiting were significantly less frequent in the infusion group. One patient given ephedrine by infusion (5%) experienced nausea compared with nine patients in the control group (36%) who had nausea and/or vomiting ($p < 0.005$). The lowest SBP of patients with nausea and/or vomiting in the control group was no lower than those without (96.4 ± 10.8 torr versus 95.4 ± 10.5 torr, $p > 0.1$).

In all neonates, the 1- and 5-minute Apgar scores were greater than 7, and time for onset of sustained rhythmic respiration was less than 90 seconds. Results of pH, P_{O_2}, P_{CO_2}, and base deficit of maternal arterial, umbilical venous, and umbilical arterial blood are shown in Table 2. There were no statistically significant differences between the two groups with regard to Apgar scores, time for onset of rhythmic respiration, blood gas tensions, or acid-base status. In each group, two neonates had a pH of umbilical venous

TABLE 2

Maternal and Fetal Acid-Base Status and Blood Gas Tensions*

	Infusion group	Bolus injection (control) group
Maternal arterial blood		
pH	7.43 ± 0.03	7.44 ± 0.03
P_{O_2} (torr)	173 ± 45	155 ± 52
P_{CO_2} (torr)	26.6 ± 3.0	27.1 ± 3.5
Base deficit	4.3 ± 2.2	3 ± 2.3
Umbilical venous blood		
pH	7.34 ± 0.04	7.36 ± 0.05
P_{O_2} (torr)	28 ± 6	30 ± 6
P_{CO_2} (torr)	37.4 ± 4.2	38.3 ± 5.4
Base deficit	4.8 ± 2.1	3.4 ± 2.8
Umbilical arterial blood		
pH	7.26 ± 0.03	7.28 ± 0.06
P_{O_2} (torr)	15.0 ± 5.7	15.5 ± 3.1
P_{CO_2} (torr)	50.2 ± 5.4	50.1 ± 5.1
Base deficit	5.2 ± 2.2	4.0 ± 3.1

* Values are means ± SD. There were no statistically significant differences between the two groups.

blood less than 7.30 (7.26, 7.26, 7.28, and 7.28). There was no correlation between maternal blood pressure and umbilical venous pH, umbilical arterial pH, umbilical venous P_{O_2}, or umbilical venous P_{CO_2}.

Discussion

It is generally agreed that maternal hypotension during conduction anesthesia should be treated promptly and aggressively (9). As treatment is usually initiated when SBP reaches 100 torr and/or 70% to 80% of the original level (10), we compared one group of patients who received conventional treatment (10) with another group of patients who received prophylactic ephedrine infusion to prevent decrease in SBP. We chose the percentage changes in SBP for treatment of hypotension because the percentage decrease in uterine blood flow correlates with the percentage decrease in, not the absolute value of maternal blood pressure (11).

Ephedrine, administered as a bolus, is commonly used to treat hypotension. With this approach, significant hypotension must inevitably exist for a period of time until the blood pressure is stabilized. On the other hand, if ephedrine is given as a bolus before hypotension occurs, some patients may develop reactive hypertension from unnecessary vasopressor.

Various approaches to the treatment and prevention of postspinal hypotension have been suggested. Gutsche (6) administered ephedrine, 50 mg, intramuscularly before spinal anesthesia and reported that SBP did not decrease more than 10% below the control

level. Reactive hypertension did occur, however, and the average increase in SBP was 16% above base line values. The disadvantages of the intramuscular route of administration of ephedrine are mainly the unpredictable absorption and the difficulty in predicting the peak effect of the vasopressor. Clark and Brunner (8) used an intravenous infusion of dopamine, but reactive hypertension occurred in 25% of their patients and umbilical oxygen tension was reduced compared with a group of patients whose mothers were treated with bolus injections of ephedrine. Mathru and associates (7) investigated the effect of prehydration with 5% albumin on spinal hypotension. Blood pressure was well maintained with this technique. However, the cost of albumin solution, and the possible risk of overloading patients with unrecognized marginal cardiovascular reserve are disadvantages of this approach.

The use of ephedrine as a continuous infusion titrated against maternal blood pressure appears to offer advantages compared with the above methods. The total dose of ephedrine and the total fluid load are similar to those used in cases treated by bolus injection of ephedrine. With an infusion of ephedrine, the drug dosage is readily controlled and altered to meet the clinical situations. If additional treatment is needed, supplemental bolus injection(s) of ephedrine can be used, but this should occur infrequently once experience with the infusion is obtained. Ephedrine can be delivered accurately by a rate-controlling device. Although manual control of ephedrine infusion is not as accurate, it is practical, efficient, and safe as the purpose of ephedrine infusion is to maintain blood pressure, which requires constant monitoring and instant changes in the infusion rate. In our patients given infusions of ephedrine, the dosage of ephedrine was titrated to maintain SBP within 90% to 100% of base line value, and thus dramatic changes in pressure were not observed. The maternal benefit of our approach was evident in the decreased incidence of nausea and vomiting.

Although maternal blood pressure was maintained nearer the BSBP with an infusion of ephedrine than with a bolus injection, umbilical blood gas tensions and acid-base states were similar. This is not surprising because the hypotension in the control group was transient and we preloaded all patients with at least 1 L of lactated Ringer's solution shortly before induction of spinal anesthesia; the risk of fetal acidosis in such a situation is therefore small (12). The fetal

outcomes for our two groups were comparable to those of other investigators (13–17) using general or epidural anesthesia.

In summary, prophylactic intravenous infusion of ephedrine was safe and effective in healthy parturients undergoing cesarean section under spinal anesthesia for the maintainance of maternal blood pressure close to base line level without causing significant maternal tachycardia, hypertension, nausea, and/or vomiting, or fetal compromise.

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Morphine Increases Myocardial Infarction Size in Rats

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MARKIEWICZ, W., FINBERG, J.P.M., AND LICHTIG, C.: Morphine increases myocardial infarction size in rats. Anesth Analg 1982;61:843–6.

Morphine anesthesia is often recommended in patients with reduced cardiac reserve. As the effect of morphine on the balance between myocardial oxygen supply and demand is not well understood, the effect of large doses of morphine (3 mg/kg, subcutaneously) on experimental myocardial infarction size in the rat was evaluated. Morphine was administered 10 minutes before thoracotomy and coronary artery ligation. Myocardial infarction size was assessed by histologic techniques 48 hours later. Rats given morphine developed significantly larger infarctions than did rats receiving an injection of saline (45.8% of left ventricular area versus 35.3%, $p < 0.05$). The data indicate that morphine increases the area of myocardial ischemia when administered before coronary artery occlusion in rats.

Key Words: ANALGESICS: morphine; HEART: myocardial infarction.

MORPHINE anesthesia has been recommended and widely used for patients with limited cardiac reserve undergoing major surgery (1, 2). Many such patients have coronary artery disease and therefore it is important to evaluate the effect of morphine on the balance between oxygen supply and demand of the myocardium. In a previous study, we evaluated the effect of morphine (1 mg/kg IV) on experimental myocardial ischemia in the anesthetized open-chest cat (3). Utilizing epicardial ST-T segment mapping to assess myocardial ischemia, we showed that morphine injected 5 minutes before coronary artery occlusion was associated with a significantly greater increase in ST-segment elevation after left anterior coronary artery occlusion than was saline injected in control animals. The ST-segment mapping has certain limitations in the measurement of infarct size (4), and other methods have been developed to assess this parameter quantitatively. In this study, we utilized histologic techniques to evaluate the effect of morphine on experimental infarction size in the rat.

Methods

Two sets of experiments were performed.

Effect of Morphine in Rats with Coronary Artery Ligation

Male Sprague-Dawley rats, weighing 180 to 333 g each, were randomly allocated to a control group or to a morphine-treatment group. Rats assigned to the morphine group received a subcutaneous injection of morphine hydrochloride, 3 mg/kg, 10 minutes before anesthesia. Rats assigned to the control group received a subcutaneous injection of normal saline. The animals were lightly anesthetized with ether, intubated, and ventilated with a mixture of room air and ether to maintain light anesthesia. Following opening of the left chest and pericardium, the left coronary artery was tied 2 to 3 mm from its origin and the chest closed (5, 6). The animals were ventilated with room air until they woke up and breathed spontaneously. They were then extubated and left to recover. The time interval from drug administration to extubation was 20 to 30 minutes. No specific monitoring was performed following extubation and no obvious difference in waking-up time from anesthesia or breathing pattern was noted between the two groups of animals under study following extubation. Forty-eight hours later, i.e., when the necrotic process is expected to peak (6), the animals were killed. The heart was removed immediately, cleaned with normal saline, and placed in 10% formalin for fixation. The left ventricle was sectioned in three slices from apex to base with cuts parallel to the atrioventricular groove. Paraffin-embedded sections were prepared from each slice, stained with hematoxylin-eosin, projected onto

a screen, and the cross-sectional area of the left ventricle and of the infarcted myocardium determined by planimetry. The fraction of left ventricular infarction was calculated as a mean of the value of three slices and expressed as a percentage of total left ventricular cross-sectional area (6). Histologic examination was performed in a blind fashion by an experienced pathologist.

Influence of Morphine on Heart Rate and Blood Pressure

Arterial blood pressure was monitored from an indwelling catheter in another group of conscious, unrestrained rats. The catheter was composed of a 3.0-cm piece of fine polyethylene tubing (0.8 mm o.d., 0.4 mm i.d.), connected to a 6-cm piece of wider tubing (0.96 mm o.d., 0.58 mm i.d.). Rats were anesthetized with ether, the fine end of the catheter inserted into the left common carotid artery and passed down to a point just above the junction of the carotid artery and aorta. The other end of the catheter was passed under the skin to an exit point at the back of the neck and stoppered with steel wire. Blood pressure recording was performed 24 hours after the operation by connecting the catheter to a P23Db pressure transducer via a 60-cm length polyethylene tubing. Heart rate was measured from the blood pressure trace. The animals were allowed to settle down for 45 minutes and then saline was injected subcutaneously. Blood pressure was followed for 60 minutes and then morphine hydrochloride (3 mg/kg) was injected subcutaneously in the same volume as the saline injection. Blood pressure was monitored for another 60 minutes after the morphine injection. The control data include experiments in which only saline was injected.

Statistical Analysis

The fraction of infarcted left ventricular myocardium in control and morphine-treated rats was compared using unpaired Student's t-test. The influence of morphine and saline on heart rate and blood pressure was assessed using Student's paired t-test.

Results

Of 50 rats surviving the operation, nine died less than 48 hours after operation (five in the control group and four in the group given morphine) leaving 41 rats available for histologic examination (21 in the control group and 20 in the group given morphine). The mean area of infarcted left ventricle was 35.3% ± 3.7% (SEM) in the control rats versus 45.8% ± 3.1% in the rats given morphine. This difference in infarction size between the two groups is statistically significant ($p < 0.05$).

The effect of morphine on systemic blood pressure and heart rate of the conscious rat is shown in the Table. The dose of morphine used caused a slight but significant reduction in both pressure and rate 30 minutes after injection, but by 1 hour after injection, blood pressure and heart rate were insignificantly different from control values.

Discussion

In this study we used histologic techniques to evaluate myocardial infarction size in the rat. This technique is widely used to evaluate the effect of various interventions on myocardial infarction size (6, 7). Our results show that, in the anesthetized rat, coronary occlusion caused significantly larger areas of left ventricular necrosis in animals pretreated with morphine when compared with control rats. We did not evaluate the influence of morphine on the rate of healing of the infarction in this study.

The mechanism by which morphine magnifies the infarction size produced by coronary artery ligation is unknown but presumably involves imbalance between the demand and supply of oxygen to the myocardium. Morphine effects on the circulation are complex and could affect the relationship between

TABLE

Effect of Morphine on Blood Pressure and Heart Rate of Conscious Rats*

	Control (n = 7)			Morphine-HCl (n = 9)		
	Preinjection	30 min	60 min	Preinjection	30 min	60 min
Mean blood pressure (mm Hg)†	117.3 ± 5.6	122.6 ± 8.9	122.1 ± 6.3	116.8 ± 4.8	110.3 ± 3.3‡	117.9 ± 3.5
Heart rate (beats/min)	344.7 ± 21.0	353.0 ± 24.7	353.3 ± 24.8	371.1 ± 18.4	321.7 ± 19.8‡	344.8 ± 14.1

* Values are means ± SEM.
† Mean blood pressure = diastolic pressure + (pulse pressure ÷ 3).
‡ $p < 0.05$.

myocardial oxygen supply and demand in various deleterious ways:

1. Morphine might affect coronary flow. It has been shown that morphine increases coronary resistance and decreases coronary flow in the intact dog (8). Such an effect was not noted after general anesthesia and is believed to be mediated through alpha-adrenergic stimulation.

2. Morphine might affect hemodynamic parameters which have a profound influence on myocardial oxygen consumption (9). Morphine-induced reduction in heart rate, and presumably in preload, would tend to reduce myocardial oxygen consumption and therefore the degree of myocardial ischemia (10, 11). The effects of a transient reduction in afterload induced by morphine are more difficult to assess. Reduced coronary perfusion secondary to hypotension is detrimental whereas reduced impedance to left ventricular emptying reduces left ventricular work and myocardial oxygen requirements. The net effect on myocardial ischemia and myocardial infarction size depends on the mode of intervention and on the model used (9-13). We showed in a previous study, (3) performed in anesthetized cats, that morphine increases ST-segment elevation independent of any change in heart rate, preload, or afterload, therefore suggesting that another mechanism is responsible for the evidence of encreased myocardial ischemia after morphine administration.

3. Morphine might affect myocardial inotropism. Although studied extensively, the effect of morphine on myocardial contractile state is not perfectly understood. Studies in papillary muscle preparations show that morphine has a negative inotropic effect (14). Most reports in the intact animal have demonstrated an increase in myocardial contractile state after administration of morphine. Thus, in the conscious dog, Vatner et al (8) demonstrated a positive inotropic effect mediated through beta-adrenergic receptors. After beta-adrenergic effects were prevented by propranolol, a slight negative inotropic effect was demonstrated. Similarly, in the anesthetized dog maintained on cardiac bypass, Vasko et al (15) showed a positive inotropic effect attributed to a sympathoadrenal discharge. Other evidence is available to indicate that morphine causes sympathoadrenal stimulation (16). Such stimulation might, by increasing myocardial contractility and therefore myocardial oxygen demand, cause an increase in myocardial infarction size (9).

Although the hemodynamic effects of morphine have been extensively studied in man, few studies have examined the effect of the drug on myocardial oxygenation. Kistner et al (17) studied 12 anesthetized subjects undergoing coronary artery bypass surgery and compared the effects of morphine and halothane on several indices of myocardial oxygen supply and demand. In their study, Kistner et al showed that morphine caused an increase in the tension-time index, in the rate-pressure product, and significant ST-segment depression of the V_5 lead of the electrocardiogram suggesting myocardial ischemia. Sethna et al (18) reported recently on 11 adult patients with significant coronary artery disease and normal left ventricular ejection fraction who were studied before and 30 minutes after infusion of morphine, 0.25 mg/kg IV. No evidence of global myocardial ischemia was noted following administration of morphine (18).

Similar doses of morphine might produce different hemodynamic effects in the animal and in man. Thus, rodents are much less susceptible to many of the pharmacologic effects of morphine than is man. The lethal dose of morphine in the rat (LD_{50}) is as high as 237 to 572 mg/kg (intravenous and subcutaneous, respectively), whereas the ED_{50} for analgesia is in the region of 0.2 to 8 mg/kg, depending on the mode of administration and on the model used to assess analgesia (19, 20). Therefore, 3 mg/kg of morphine is not a large dose in the rat although it caused significant hemodynamic changes in the animals under study.

In summary, we found that morphine in large doses (3 mg/kg) increased the size of infarction caused by coronary artery ligation in the rat. Because similar large doses of morphine are used in the human with coronary artery disease undergoing a variety of surgical procedures, our findings suggest that further investigation of the effect of morphine on myocardial oxygen indices should be performed in man.

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Gallamine Administered by Combined Bolus and Infusion

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SHANKS, C. A., FUNK, D. I., AVRAM, M. J., AND HENTHORN, T. K.: Gallamine administered by combined bolus and infusion. Anesth Analg 1982;61:847–52.

A technique combining an intravenous bolus and intravenous infusion regimen of gallamine based on its pharmacokinetics was developed to produce continuous relaxation during surgery. The combination of a bolus dose of gallamine, 2.5 mg/kg, and infusion, 0.8 mg/kg/hr, was tested in 11 patients. In 10 patients, surgery continued long enough to allow demonstration of an apparent plateau in the serum gallamine concentrations. At the cessation of the infusion, the mean gallamine concentration of 11.8 μg/ml was associated with an average paralysis intensity of 92%. Pharmacokinetic analysis of the gallamine serum concentration-time data was fitted to a three-compartment model. In this study of 50- to 76-year-old patients, the most striking difference from other studies was that the elimination half-life averaged 247 minutes in this study whereas 128 to 141 minutes has been reported previously.

Key Words: NEUROMUSCULAR RELAXANTS: gallamine; PHARMACOKINETICS: gallamine.

G ALLAMINE triethiodide has been used as a non-depolarizing neuromuscular blocking agent for more than three decades. Although its administration by continuous infusion was reported soon after its introduction into clinical anesthesia (1), only recently could a pharmacokinetic rationale be developed for this technique. The pharmacokinetics of gallamine in man has been reported to show multicompartmental behavior following administration by intravenous bolus (2–5); Agoston and colleagues (3) confirmed in man that gallamine was primarily excreted unchanged in the urine. They found also that poor urinary excretion did not result in persistent high serum concentrations and prolonged duration of neuromuscular blockade, which they explained as due to drug redistribution.

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The purpose of the present study was to: (a) predict a bolus and infusion regimen for gallamine, based on its pharmacokinetics; (b) reexamine its pharmacokinetics under these circumstances; and (c) relate creatinine and gallamine renal clearance rates.

Methods

Eleven adult patients were studied during elective surgery for arterial disease below the aorta. Clinical preoperative details are shown in Table 1. Institutionally approved written informed consent was obtained the day before surgery. The patients had no known renal, hepatic, or neuromuscular disease, and none were receiving drugs known to affect neuromuscular transmission.

Following an intramuscular narcotic premedication, anesthesia was induced with thiopental, 100 to 300 mg, droperidol, 5 to 10 mg, and fentanyl, 50 to 100 μg, administered via a peripheral intravenous catheter. Further increments were added as required for supplementation of nitrous oxide anesthesia. Before the administration of gallamine, samples were obtained from the radial arterial and urinary catheters. Ventilation with nitrous oxide in oxygen was adjusted to maintain the arterial carbon dioxide tension close to 35 mm Hg. Crystalloid solutions were administered intravenously as required to maintain fluid balance and cardiovascular stability. No diuretics were admin-

istered before or during the gallamine infusion; however, intraoperative arteriography after the infusion was followed by a diuresis.

The dosage regimen for gallamine was calculated from pharmacokinetic data derived previously (5). The bolus dose was calculated by multiplying the desired plasma drug concentration by the volume of distribution; multiplication of the desired plasma drug concentration by the plasma clearance gave the infusion rate (6). These calculations indicated that the initial dose of gallamine should be 2.5 mg/kg followed by an infusion rate of 0.8 mg/kg/hr (Table 2). In prediction, this bolus dose and infusion rate were combined with previous mean data (5) and fitted to the bolus and infusion equation used in a similar study with pancuronium (7) for an infusion time of 120 minutes. The predicted serum gallamine concentration versus time relationship was compared visually with that actually measured.

Following the commencement of the gallamine infusion, arterial blood was collected at intervals for the next 12 hours. Timed urine collections were made, usually every 30 minutes, throughout the infusion. Serum and urine samples were stored at $-30°C$ for

later measurement of creatinine and gallamine concentrations.

Serum and urine creatinine concentrations were assayed using a modified Jaffé reaction (8, 9). Total serum gallamine concentrations were determined by the spectrofluorimetric technique of Kersten et al. (10) modified for use with gallamine (5). Neglecting the 1st hour of the infusion, to allow for redistribution, the infused gallamine dosage was compared with the total amount of drug obtained in the urine for each 20- to 30-minute collection period of the infusion. Estimates of simultaneous creatinine and gallamine renal clearances made for these periods were compared by linear regression analysis (11). The pharmacokinetic parameters for gallamine were derived from the serum concentration-time data. Preliminary analysis indicated that a triexponential curve was required to characterize the distribution and elimination of gallamine. Accordingly, we analyzed the kinetics of these processes with a three-compartment open model. Calculations were made with the SAAM 23 digital computer program developed by Berman and Weiss (12) and implemented on a Control Data Corporation model 6400 computer.

The effect of gallamine on neuromuscular transmission was used to assess the pharmacodynamics. Following induction of anesthesia, subcutaneous needle electrodes were inserted at the elbow, and the ulnar nerve was stimulated supramaximally for 0.1 msec every 10 seconds. The compound electromyogram from the first interspace of the hand was recorded; the intensity of neuromuscular blockade was assessed by comparison of the response with its drug-free control.

TABLE 1
Patient Characteristics

Age	Sex	Weight	Surface area*	Blood urea nitrogen†	Creatinine†
yr		kg	m²	mg/100 ml	
62	F	53	1.56	11	0.7
76	M	100	2.24	19	1.2
67	F	65	1.75	13	0.9
71	M	72	1.87	18	1.2
51	F	68	1.79	15	0.8
58	M	73	1.86	18	1.2
57	M	86	2.13	16	0.9
50	F	60	1.62	18	1.3
65	M	70	1.89	21	1.3
66	M	84	2.02	10	1.0
67	M	58	1.64	15	0.9

* Derived from $Wt^{0.425} \times Ht^{0.725} \times 71.84$.

† Normal ranges: blood urea nitrogen, 0 to 20 mg/100 ml; creatinine, 0 to 1.7 mg/100 ml.

TABLE 2
Calculation of Gallamine Bolus and Infusion Regimen*

Apparent volume of distribution (area)	225 ml/kg
Plasma clearance rate	72 ml/hr/kg
Desired gallamine concentration	11 mg/L
Calculated bolus dose	2.5 mg/kg
Calculated infusion rate	0.8 mg/kg/hr

* From Ramzan et al[5] and Mitenko and Ogilvie.[6]

Results

In nine patients the infusion of gallamine was continued for 2 hours or more. In none of the patients was difficulty encountered in reversing the effects of gallamine; neither did they develop tachycardia, even following the bolus dose of gallamine.

Due to the brevity of surgery, one patient did not reach "steady state" in 75 minutes of infusion. The other 10 patients showed an apparent plateau in serum gallamine concentrations; at the end of the infusion the mean concentration was 11.8 ± 2.4 (SD) $\mu g/$ ml and was associated with an average 92% $\pm$ 9% paralysis. In the patient who was least relaxed (73% paralysis), the serum gallamine concentration at the end of the infusion was 12.3 $\mu g/ml$.

Redistribution of the initial bolus dose was appar-

FIG 1. Typical record of serum concentrations of gallamine during its infusion and for following 12 hours (patient 1). Dashed line indicates intraoperative depression of electromyogram twitch response; scale representing percent paralysis is shown at 5-hour mark, 1 hour after surgery.

ently complete in most patients by the end of the 1st hour. Following the redistributive phase, serum drug concentrations and the intensity of paralysis tended to vary in parallel fashion during the infusion. As in Fig 1, some 20 minutes after cessation of the infusion the intensity of neuromuscular blockade began to diminish. Surgery usually was concluded before full recovery from paralysis, precluding full assessment of the concentration-response relationships.

The total serum gallamine time plot predicted from the bolus and infusion equation (7) together with the experimental results from the 11 patients in the study is shown in Fig 2. During the infusion, the mean values observed were almost identical with those predicted by the bolus and infusion equation calculated with data from a previous study (5). Each patient's plasma concentration data were analyzed with a three-compartment open mammillary model (Fig 3). Estimates of the pharmacokinetic parameters for each patient are shown in Table 3.

The percentage of gallamine excreted in the urine during steady state ranged from 15% to 122% (64% ± 33%). Slow rates of renal excretion did not necessarily entail concurrently high serum concentrations of gallamine. During the apparent plateau phase, the renal clearances of ceratinine and gallamine were compared. Linear regression analysis, with creatinine clearance as the independent variable, gave the equation $y = 0.22x + 23.6$ ($r = 0.79$, $p < 0.001$), as shown in Fig 3.
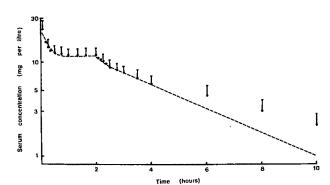
FIG 2. Time course of serum concentrations of gallamine was predicted for a 2-hour infusion of gallamine (dashed line). Superimposed are mean ($\pm$SD) values observed in 11 patients, recommencing the postinfusion time scale at 2 hours. Some standard deviations were omitted for visual purposes; these are of same order of magnitude as their neighbors.

Discussion

Pharmacodynamic and pharmacokinetic studies involving a loading dose and infusion technique have been reported for administration of pancuronium (7), d-tubocurarine (13, 14), and ORG NC 45 (15). As was observed with gallamine, these studies demonstrated a relationship between the apparent plateau in the plasma concentration of neuromuscular blocking agent and the depression of twitch response. The relationship between plasma relaxant concentration and effect at equilibrium closely resembles that found following bolus dosage (16). In the present study, prediction of a desired steady-state concentration was

transferred from data obtained in bolus studies (Table 2). Assuming the usual sigmoid curve exists for gallamine concentration and effect, then it is not surprising that paralysis averaged 92%; at the upper end of the curve there are smaller changes in paralysis for similar increases in concentration. Although international differences have been reported for the effects of d-tubocurarine (17), the mean data for gallamine derived elsewhere gave a bolus and infusion regimen that could be used in this country. The pharmacokinetics of gallamine in this bolus and infusion study were fitted to a three-compartment open mammillary
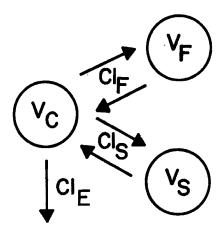
FIG 3. Schematic diagram of three-compartment open model, with its central, fast, and slow compartments. Reversible drug distribution occurs from the central volume (V_C) into two peripheral spaces: one is "shallower" or "faster" (V_F) and one is "deeper" or "slower" (V_S). Elimination clearance (Cl_E) is from central compartment. Fast and slow clearances (Cl_F and Cl_S) are products of their respective intercompartmental rate constants and their volumes.

model. When a three-compartment model was used to characterize the kinetics of gallamine distribution, previous investigators (3, 4) obtained distribution volume estimates that were similar to ours. The three-compartment structure of this model reflects the heterogeneity of transcapillary exchange from intravascular space to the interstitial fluid space (18). Two other bolus-dosing studies (2, 5) have reported the disposition of gallamine with two-compartment models; these have total volumes of distribution similar to those shown in Table 3.

The most striking difference between all these studies and the results in Table 3 is that our patients show a considerable prolongation over the mean elimination half-lives previously reported (128 to 141 minutes). As the distribution volumes are in good agreement, this difference must be due to a reduced plasma clearance in our patients. Reduced plasma clearance could be due in part to the effects of age, a factor that has been implicated in the reduced elimination of pancuronium (19). However, no correlation was found between the age of the patient and the excretion rate of gallamine in 15 patients (3). Pooling the data from several studies (2, 5, 20) with those in Table 3 allowed the relationship to be examined for 48 patients by linear regression analysis. There was a significant correlation between age and plasma clearance ($r = 0.31$, $p < 0.05$) and between age and elimination half-life ($r = 0.54$, $p < 0.001$). With half-life as the independent variable, the latter equation was $y = 1.45x + 103$. The longer elimination half-life in our study did not greatly affect the ability of the model to predict the mean steady-state plasma concentration

TABLE 3

Pharmacokinetics of Gallamine in 11 Patients

Patient no.	Compartmental volumes					Clearances†			Elimination half-life
	V_C	V_F	V_S	V_{TOT}·	V_{TOT}/kg	Cl_F	Cl_S	Cl_E	
			L				*ml/min*		*hr*
1	0.564	5.06	10.29	15.91	0.297	235	51	58	4.6
2	7.05	17.68	13.13	27.89	0.379	1130	60	115	5.2
3	3.63	6.48	9.87	19.97	0.307	447	64	51	5.2
4	5.81	7.62	5.63	19.06	0.265	359	28	60	4.0
5	1.16	5.09	6.87	13.12	0.193	439	58	68	3.0
6	4.76	3.91	7.60	16.27	0.224	418	91	60	3.25
7	6.99	10.48	16.26	33.73	0.390	1000	33	100	3.23
8	3.99	3.14	5.25	12.38	0.204	208	41	33	4.5
9	6.28	4.43	9.60	20.36	0.291	674	103	69	4.0
10	4.17	6.40	11.64	22.21	0.264	522	115	70	4.4
11	4.84	6.98	7.76	19.58	0.336	653	55	78	3.92
Mean	4.48	7.03	9.45	20.95	0.291	553	64	70	4.12
(±SD)	(2.13)	(4.06)	(6.80)	(8.00)	(0.065)	(293)	(26.7)	(22.3)	(0.75)

* V_{TOT} is the sum of the central (V_C), fast (V_F), and slow (V_S) compartment volumes.

† Abbreviations are: Cl_F, fast; Cl_S, slow; and Cl_E, elimination clearances, respectively.

of gallamine (Fig 2), although a true steady state could not have been achieved in the time available for the infusion. A prolonged elimination half-life does, however, imply that the paralytic effects of an overdose of gallamine would persist longer in those patients with slow elimination.

When ¹⁴C-labeled gallamine was administered to dogs (21), an average of 30% of the radioactive material was eliminated in 15 minutes, apparently as unchanged gallamine; total elimination was approached in approximately 4 hours. In man, using spectrofluorimetric measurement, Agoston and colleagues (3) reported that 15% to 100% could be recovered from the urine collected in the subsequent 30 hours. Although of very different design, our study also showed a considerable range in the percentage of drug recoverable from the urine. The steady-state renal clearance of gallamine was approximately one quarter that of creatinine (Fig 4). As the technique measures total drugs in the serum, this ratio would be higher if protein binding is significant.

The glomerular filtration rate (GFR) is not estimated accurately by creatinine clearance; with declining GFR its actual value is progressively overestimated by creatinine clearance (22, 23). GFR diminishes with advancing age (24). In young volunteers, GFR is decreased by thiopental, nitrous oxide, narcotics, and neuromuscular blocking drugs (25). As the biliary excretion of gallamine is negligible in man (3), it is inferred that these factors could combine to reduce

its renal excretion and thus its plasma clearance rate. The pharmacokinetics of gallamine in patients with chronic renal failure (26) shows a low plasma clearance rate.

Although the literature often assumes a relationship between gallamine excretion and GFR, this appears to be by inference only. The kinetics of inulin and gallamine have been studied after simultaneous injection in anesthetized dogs (18). Comparison of the simultaneous clearances by linear regression indicates that mean clearance for gallamine was two thirds that of inulin in these animals. Underestimation of GFR by gallamine and its overestimation by creatinine are likely to have combined to produce the low value for the slope of the regression line shown in Fig 4.

In conclusion, this study shows that it was possible to take the pharmacokinetic and pharmacodynamic data for gallamine obtained in a bolus study, and transfer this to calculate a bolus and infusion regimen that was adequate for production of surgical relaxation. The clearance of the relaxant was lower than expected. Although this had minimal impact within the time span of the infusion, it does show that individuals vary in drug disposition and indicates a need to monitor the intensity of relaxation in each patient.

CLEARANCES   ml/min

Fig 4. Comparison of total renal clearances of creatinine and gallamine based on data obtained during plateau in serum gallamine concentrations.

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Alteration of Renal Hemodynamics by Thiopental, Diazepam, and Ketamine in Conscious Dogs

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PRIANO, L. L.: Alteration of renal hemodynamics by thiopental, diazepam, and ketamine in conscious dogs. Anesth Analg 1982;61:853-62.

Renal hemodynamic changes associated with thiopental, diazepam, and ketamine were studied in conscious dogs after previous surgical placement of an aortic catheter and a Doppler ultrasonic flow probe on the left renal artery. Thiopental, 10 mg/kg, changed blood pressure minimally whereas 20 mg/kg significantly decreased blood pressure by 5% to 10%. Renal blood flow initially increased significantly, then returned to control levels after both doses. Renal resistance was not significantly altered by 10 mg/kg of thiopental whereas 20 mg/kg significantly reduced resistance by 10%. Diazepam, 1 and 2 mg/kg, caused transient increases in arterial pressure of approximately 10%. Renal blood flow significantly decreased 5% to 10% from control levels with both doses. Renal resistance did not change with the 1-mg/kg dose of diazepam, but 2 mg/kg of diazepam increased it by 8% to 12%. Ketamine, 2.5 and 5 mg/kg, elevated arterial pressure 20% to 40%. Renal blood flow increased significantly by 10% to 15% with both doses of ketamine. This effect lasted longer with the larger dose. Renal resistance was significantly elevated by the 2.5-mg/kg dose of ketamine, whereas 5 mg/kg did not alter this variable. In conclusion, each of these drugs maintains renal blood flow reasonably well in an unanesthetized animal. However, ketamine appears to be more beneficial than thiopental, which in turn, is superior to diazepam in this regard. Little dose-response effect was evident for any of the drugs. Furthermore, it should be noted that changes in arterial pressure can be misleading when perfusion of this vascular bed is considered.

Key Words: KIDNEY: blood flow; ANESTHETICS, Intravenous: thiopental, ketamine, diazepam; HYPNOTICS: benzodiazepines, diazepam.

MANY REPORTS are available on the hemodynamic effects of thiopental (1-3), diazepam (4-10), and ketamine (11-17). However, relatively little is known about the effects of these drugs on the hemodynamics of individual organs, particularly the kidney. One study that used the xenon wash-out method in conscious dogs to determine the effects of thiopental or pentobarbital on renal blood flow, found that both drugs significantly decreased renal blood flow (18). Another study utilizing para-amino hippurate (PAH) clearance to measure effective renal plasma flow (RPF) found that diazepam decreased RPF in

children with various forms of renal disease but did not affect RPF in pentobarbital-anesthetized rabbits (19). Three studies have examined the effects of ketamine on renal blood flow: two in anesthetized dogs (20, 21) and one in conscious rats (22). Hirasawa and Yonezawa (20) used a thermoelectric flowmeter and found that ketamine slightly, but significantly, decreased both renal cortical and renal medullary blood flows. Bevan and Budhu (21) used PAH clearance to conclude that ketamine does not affect renal hemodynamics, a finding supported by Idvall et al (22), using a microsphere technique in rats.

Other than these studies, few data exist concerning the important effects of anesthetic induction agents on renal hemodynamics. The object of this study was to examine alterations in renal hemodynamics following bolus administrations of thiopental, diazepam, and ketamine. We used conscious, chronically instrumented animals whose cardiovascular systems were not obtunded by the acute effects of recent surgery or by the simultaneous presence of other anesthetic

agents, both of which can modify circulatory responses. In addition, we utilized a method of measuring renal blood flow that would allow continuous and instantaneous readout during the entire period of observation.

Methods

This study was performed in 23 healthy mongrel dogs of either sex, weighing 20 to 30 kg each. Under halothane-nitrous oxide-oxygen anesthesia, a Doppler ultrasonic flow probe, 4 to 6 mm in diameter, (L&M Electronics, Daly City, CA) was placed around the left renal artery and a small heparin-filled Tygon catheter was positioned in the abdominal aorta via a lumbar artery. The instrumentation wires and catheter were run subcutaneously and exteriorized at an intrascapular site on the animal's back,. The animal then recovered for 10 to 14 days before the drug studies were initiated. During this time, the arterial catheter was flushed and filled with a heparin solution, 1000 units/ml, three times weekly.

Aortic pressure was measured via the previously implanted Tygon catheter, with a mercury-calibrated Statham P23ID strain gauge manometer (Statham Instruments Inc, Oxnard, CA). Renal blood flow was measured using the previously implanted flow probe, which was connected by a hard-wire system to a model 1012 Doppler ultrasonic flow meter (L&M electronics). This system had an accurate electronic zero and its calibration for volume flow has been previously described (23). Phasic and mean arterial pressures and phasic and mean renal blood flows were recorded on a direct writing oscillograph (Gould-Brush, Cleveland, OH). Renal vascular resistance was calculated as the quotient of mean arterial blood pressure in millimeters of mercury and mean renal blood flow in milliliters per minute. During the 10- to 14-day recovery period following surgery, the animals were given table training several times per week while their catheters were flushed. Here they learned to lie quietly on the experiment table. Also, this interval of time was sufficient for the animals to regain their presurgical vigor and to allow tissue growth to occur under and around the flow probes.

At the time of an experiment, with the animal resting on its right side, a peripheral intravenous catheter was inserted into a foreleg vein. Control or base line measurements of cardiovascular function were then recorded for a sufficient period of time to assure that a steady state had been reached. At that point, a bolus dose of one of the three drugs in question was administered over 30 seconds. Thiopen-

tal was given in 10- and 20-mg/kg doses, diazepam in 1- and 2-mg/kg doses, and ketamine in 2.5- and 5-mg/kg doses. Changes in arterial pressure, renal blood flow, and renal vascular resistance, from the awake control values, were recorded at 1, 3, 5, 7, 10, 15, 20, and 30 minutes. Changes at each of these times were compared statistically with the base line values by use of Student's paired t-test; thus, each animal served as its own control. Changes were considered to be statistically significant if a p value of less than 0.05 was obtained. Two doses of each drug were administered in an attempt to establish dose-response effects. The doses selected were chosen in the following manner. Thiopental, 10 mg/kg IV, produces a sleep time in dogs equivalent to 3 to 4 mg/kg IV in humans. Numerous previous studies have documented that 2.5 mg/kg of intravenous ketamine is equivalent to 1 mg/kg IV in humans in terms of duration of action (13–17). In the case of diazepam, 0.2 mg/kg IV is a usual induction dose for humans. Canine doses for most central depressants are 2 to 10 times greater than those in humans. Thus, 1 mg/kg was empirically selected for the lower diazepam dose for the dog. All doses were then doubled for purposes of the dose-response aspect of the study. The dosage sequence was randomized. After an animal received either dose of ketamine or thiopental, an interval of 24 hours elapsed before additional experiments were performed. A period of 48 hours was allowed to elapse following an administration of diazepam. For technical reasons, it was difficult to keep all the instrumentation working perfectly in all the animals during the course of the study. Thus, there is some difference between the number of animals in each drug dose group.

Results

In the figures and table, data are given for a 30-minute period after a bolus administration of each drug. Control values are expressed as mean actual values ± SEM. Changes are expressed as mean percent change from control values. Comparisons between drugs can be seen in the Table. For purposes of discussion, the 30-minute observation period will be divided into early (1 to 3 minutes), middle (5 to 15 minutes), and late (20 to 30 minutes) portions.

Thiopental (Figs 1 and 2 and Table)

Thiopental, 10 mg/kg (n = 10), significantly increased renal blood flow 1 minute after administration. Renal vascular resistance at this point was un-

TABLE
Renal Hemodynamic Changes in Normovolemia by Induction Agents: Thiopental (T), Diazepam (D), and Ketamine (K)*

Variable	Control values	Percentage change from control after drug administration							
		1 min	3 min	5 min	7 min	10 min	15 min	20 min	30 min
HR (beats/min)									
L T (n = 10)	84 ± 4	44 ± 8a	52 ± 12a, c	46 ± 4a, c, d	37 ± 9a, c, d	36 ± 10a, c	24 ± 7a	19 ± 7a	14 ± 12a
H T (n = 11)	94 ± 5	52 ± 4a, c	44 ± 4a, d	40 ± 5a, d	31 ± 4a, d	28 ± 5a, d	16 ± 6a, d	11 ± 5a, d	16 ± 11
L D (n = 9)	95 ± 4	24 ± 5a, e	16 ± 5a, b, e	13 ± 4a, e	14 ± 4a, e	8 ± 4b, e	9 ± 4e	7 ± 3e	3 ± 3
H D (n = 11)	88 ± 5	34 ± 5a, e	33 ± 6a, e	26 ± 5a, e	24 ± 4a, e	22 ± 5a, e	20 ± 5a, e	13 ± 4a, e	9 ± 4e
L K (n = 12)	92 ± 3	53 ± 8a	66 ± 7a	68 ± 7a	67 ± 10a	52 ± 7a	37 ± 7a	25 ± 5a, b	5 ± 8b
H K (n = 11)	93 ± 5	63 ± 11a	70 ± 11a	70 ± 12a	66 ± 9a	65 ± 10a	57 ± 10a	50 ± 11a	34 ± 6a
AoP (torr)									
L T	103 ± 4	8 ± 2a, d	6 ± 3d	4 ± 2b, d	1 ± 2b, d	0 ± 2b, d	-3 ± 2b, d	-1 ± 1b	0 ± 2b
H T	104 ± 4	17 ± 4a	3 ± 4d	-6 ± 2a, c, d	-9 ± 2a, c, d	-9 ± 2a, c, d	-11 ± 2a, c, d	-11 ± 2a, c, d	-8 ± 3a, d
L D	103 ± 3	8 ± 2a, e	0 ± 2e	-2 ± 3e	-3 ± 3e	-1 ± 3e	-4 ± 3e	-3 ± 3	-4 ± 3
H D	100 ± 3	9 ± 2a, e	7 ± 3a	3 ± 3e	2 ± 3e	1 ± 2e	-1 ± 3e	-1 ± 3e	0 ± 3
L K	103 ± 4	38 ± 7a	33 ± 7a	31 ± 6a	29 ± 7a	18 ± 5a	9 ± 4	2 ± 3	-1 ± 2
H K	102 ± 3	36 ± 10a	25 ± 9a	26 ± 10a	26 ± 9a	27 ± 9a	20 ± 8a	13 ± 6	5 ± 4
RBF (ml/min)									
L T	124 ± 6	8 ± 2a	2 ± 2	0 ± 2d	-1 ± 2d	-2 ± 2	-3 ± 2d	-4 ± 2d	-4 ± 2
H T	140 ± 10	15 ± 6a, c	6 ± 4c	4 ± 4	2 ± 4d	-2 ± 4d	-4 ± 4d	-5 ± 4d	-3 ± 5
L D	122 ± 11	1 ± 3	-3 ± 2e	-5 ± 2a, e	-6 ± 3e	-6 ± 3e	-8 ± 3a, e	-6 ± 3e	-6 ± 3
H D	121 ± 9	-4 ± 2	-3 ± 1a, e	-2 ± 2e	-4 ± 2e	-5 ± 2a, e	-7 ± 2a, e	-7 ± 3a, e	-5 ± 3
L K	113 ± 9	7 ± 5	13 ± 6a	14 ± 5a	14 ± 5a	7 ± 4	5 ± 3	3 ± 2	0 ± 3
H K	114 ± 10	2 ± 6	13 ± 7	14 ± 7	17 ± 6a	18 ± 6a	13 ± 5a	6 ± 3	1 ± 2
RVR torr/ml/min									
L T	0.83 ± 0.03	1 ± 3d	3 ± 2	4 ± 2b	1 ± 2b	2 ± 2	1 ± 3	3 ± 3b	4 ± 2
H T	0.77 ± 0.05	6 ± 7d	-1 ± 3c	-8 ± 4a, c, d	-9 ± 3a, c, d	-6 ± 4c	-6 ± 4c, d	-5 ± 1c, d	-4 ± 4
L D	0.90 ± 0.08	7 ± 4e	3 ± 2b	4 ± 2	3 ± 3	5 ± 4	5 ± 4	3 ± 3	3 ± 3
H D	0.86 ± 0.05	14 ± 2a	11 ± 3a	9 ± 4	6 ± 3	6 ± 3a	7 ± 3	8 ± 3a	6 ± 3
L K	0.96 ± 0.07	31 ± 7a	23 ± 9a	16 ± 6a	15 ± 6a	12 ± 6	4 ± 3	-1 ± 2	-1 ± 3
H K	0.96 ± 0.08	39 ± 14a	11 ± 6	11 ± 6	7 ± 6	8 ± 6	9 ± 6	6 ± 5	4 ± 4

* Values are means ± SEM. Abbreviations used are: L, low; H, high; HR, mean heart rate; AoP, mean arterial pressure; RBF, mean renal blood flow; RVR, mean renal vascular resistance. Drug doses are as follows: L T, 10 mg/kg; H T, 20 mg/kg; L D, 1 mg/kg; H D, 2 mg/kg; L K, 2.5 mg/kg; H K, 5 mg/kg. On left side of table, mean actual control values ± SEM are indicated for heart rate (beats/minute), aortic pressure (mm Hg), renal blood flow (ml/min), and renal vascular resistance (mm Hg/ml/min). After administration of each dose of each drug, the mean percent changes ± SEM from control values are indicated over 30-minute period. Italic letters a through e refer to statistical analyses: a, statistically significant changes from that group's actual control value ($p < 0.05$); b, statistically significant differences for any one drug between the low and the high doses ($p < 0.05$); c, statistically significant changes between diazepam and thiopental comparing low dose with low dose or high dose with high dose ($p < 0.05$); d, statistically significant differences between ketamine and thiopental comparing low dose with low dose or high dose with high dose ($p < 0.05$); and e, statistically significant changes between ketamine and diazepam comparing low dose with low dose or high dose with high dose ($p < 0.05$). Number of animals in each group is indicated on left side of panel in parentheses in the HR section.

THIOPENTAL-RENAL HEMODYNAMICS-Normovolemia
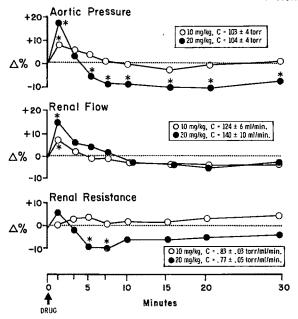
Fig 1. Thiopental and renal hemodynamics. Mean percent changes in aortic pressure, renal blood flow, and renal vascular resistance after 10 mg/kg (O) and 20 mg/kg (●) doses of thiopental. Inset for each variable indicates actual mean control values ± SEM. Control values are depicted on ordinate as 0. After drug administration, indicated by arrow, changes from control values are expressed as mean percent change and are followed for 30 minutes. Asterisks refer to statistically significant changes ($p < 0.05$) from control values.

changed. Thereafter, renal blood flow was unchanged from the control value, as was renal resistance. With thiopental, 20 mg/kg ($n = 11$), renal blood flow likewise was increased significantly at 1 minute and renal vascular resistance was unchanged. Thereafter, renal blood flow returned to levels not significantly different from the control value although renal resistance tended to be lower, significantly so at 5 and 7 minutes. Data in the Table demonstrate that there were no significant differences in effects of low and high doses of thiopental on renal blood flow. However, with the larger dose, arterial pressure decreased significantly at all time periods after 5 minutes. This was significantly different from the effect of low-dose thiopental on blood pressure. Renal resistance following high-dose thiopental was significantly less than it was after the low dose at 5, 7, and 20 minutes. An actual recording of a typical response for the high dose of thiopental is shown in Fig. 2.

Diazepam (Figs 3 and 4 and Table)

Low-dose diazepam, 1 mg/kg ($n = 9$), resulted in slight but statistically significant decreases in renal blood flow at 5 and 15 minutes. Arterial pressure increased significantly at 1 minute, but thereafter was unchanged from control levels. Renal vascular resistance remained unchanged from control levels for the

RENAL

THIOPENTAL-NORMOVOLEMIA
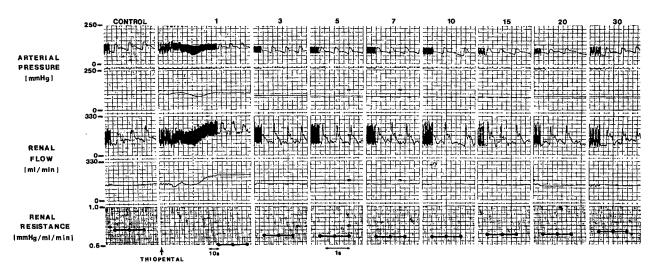
Fig 2. Actual recording of phasic and mean arterial pressure and renal blood flow during control period and after drug injection for high dose (20 mg/kg) of thiopental. Calculated renal vascular resistance is plotted in bar form in lower panel. Paper speed is indicated at bottom and can be compared using the 1-second tick marks which can be seen between two arterial pressure channels in upper panel.

DIAZEPAM - RENAL HEMODYNAMICS - Normovolemia
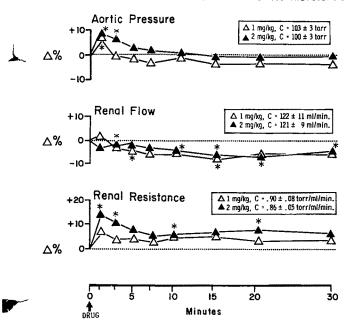
FIG 3. Diazepam and renal hemodynamics. Mean percent changes in aortic pressure, renal blood flow, and renal vascular resistance after 1 mg/kg (△) and 2 mg/kg (▲) doses of diazepam. Inset for each variable indicates mean actual control values ± SEM. Control values are depicted on ordinate as 0. After drug administration, indicated by arrow, changes from control values are expressed as mean percent change and are followed for 30 minutes. Asterisks refer to statistically significant changes ($p < 0.05$) from control values.

entire observation period. High-dose diazepam, 2 mg/kg (n = 11), significantly, but again slightly, decreased renal blood flow during the middle and late portions of the observation period. Arterial pressure increased significantly during the early observation period but then returned to levels not different from control levels. Renal resistance increased significantly during the early observation period and remained elevated at 10 and 20 minutes. A typical recorded trace for the renal vascular effects of high-dose diazepam is shown in Fig 4. With the exception of a single significant difference in renal vascular resistance at 3 minutes, there were no statistically significant dose-response differences in arterial pressure and renal blood flow for the two doses of diazepam.

Ketamine (Figs 5 and 6 and Table)

Low-dose ketamine, 2.5 mg/kg (n = 12), increased arterial pressure for the first 10 minutes of the observation period. This was accompanied by significant increases in renal blood flow. The increases in pressure were greater than the increases in flow, thus renal vascular resistance was significantly elevated for the first 7 minutes. High-dose ketamine, 5 mg/kg (n = 11), produced similar elevations in arterial pressure that lasted up to 20 minutes. Renal blood flow increased to approximately the same degree as with the low dose. Increases in renal blood flow with the

RENAL

DIAZEPAM - NORMOVOLEMIA
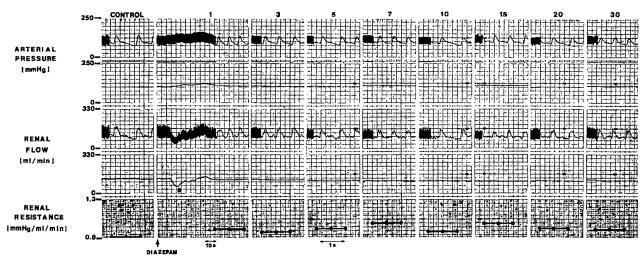
FIG 4. Actual recording of phasic and mean arterial pressure and renal blood flow during control period and after drug injection for high cose (2 mg/kg) of diazepam. Calculated renal vascular resistance is plotted in bar form in lower panel. Paper speed is indicated at bottom and can be compared using 1-second tick marks which can be seen between two arterial pressure channels in upper panel.
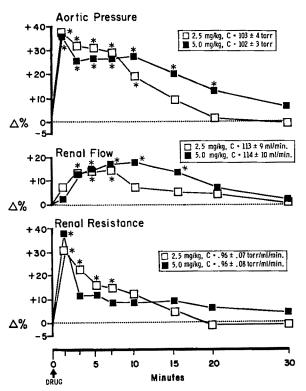
FIG 5. Ketamine and renal hemodynamics. Mean percent changes in aortic pressure, renal blood flow, and renal vascular resistance after 2.5-mg/kg (□) and 5-mg/kg (■) doses of ketamine. Inset for each variable indicates mean actual control values ± SEM. Control values are depicted on ordinate as 0. After drug administration, indicated by arrow, changes from the control values are expressed as mean percent change and are followed for 30 minutes. Asterisks refer to statistically significant changes (p < 0.05) from control values.

higher dose lasted longer than with the low dose. In contrast to the effects of low-dose ketamine, renal vascular resistance was not significantly elevated by the higher dose except at 1 minute. A typical trace for high-dose ketamine can be seen in Fig 6. As will be noted from the Table, there were no statistically significant differences in responses of arterial pressure, renal blood flow, or renal vascular resistance between the low and high doses of ketamine.

Comparisons between the effects of the three drugs show that, insofar as diazepam and thiopental were concerned (Table, c values), there were no significant differences in responses of aortic pressure, renal blood flow, or renal vascular resistance between the low doses of diazepam and thiopental. However, aortic pressure and renal resistance were significantly lower with high-dose thiopental than with high-dose diazepam. Renal blood flow was greater with thiopental than with diazepam early in the observation pe-

riod. Ketamine increased aortic pressure significantly more than thiopental with both doses (Table, d values). High-dose ketamine increased renal vascular resistance significantly more than high-dose thiopental. However, it also increased renal blood flow to a greater degree than thiopental following both low and high dosages. Ketamine increased aortic pressure to a significantly greater degree than did diazepam with both doses (Table, e values). Likewise, ketamine increased renal blood flow with both doses whereas diazepam decreased it. These differences were also statistically significant. There were no statistically significant differences in the effects of ketamine and diazepam on renal vascular resistance.

Discussion

Intravenous agents are frequently utilized because of a desire to maintain better hemodynamic stability. One cannot assume, however, that because generalized hemodynamics remain stable, i.e., arterial blood pressure and pulse rate, that individual organ hemodynamics are similarly stable. This was certainly evident in the present study. When arterial pressure increased, decreased, or remained unchanged following high doses of ketamine, thiopental, and diazepam, respectively, renal blood flow increased, remained unchanged, and decreased, respectively.

Thiopental is considered to be a cardiovascular depressant due to venodilation, decreased venous return, and depression of myocardial contractility. Subsequently, blood pressure decreases and total peripheral resistance increases reflexly (1, 2). These alterations may result from direct effects on the vasculature or indirectly from centrally mediated decreases in sympathetic outflow (24). If cardiac output decreases there must be changes in flow to various peripheral organs. However, in the present study, other than the 1st minute after drug injection, blood flow to the kidney was not affected by thiopental. Arterial pressure and heart rate increased transiently after thiopental. Our hypothesis as to why this occurred is that in a conscious animal there is an initial increase in sympathetic activity as the animal first senses the onset of drug effect. This is based on the observation that animals usually initially have proptosis and mydriasis at this time, and this has also been observed in humans (25). After this initial brief phase, the better known hemodynamic changes of thiopental were seen. Mean arterial pressure decreased. Despite the decreased perfusion pressure, renal blood flow was maintained as renal vascular resistance decreased. This could be due to direct renal arteriolar dilation

RENAL

KETAMINE-NORMOVOLEMIA
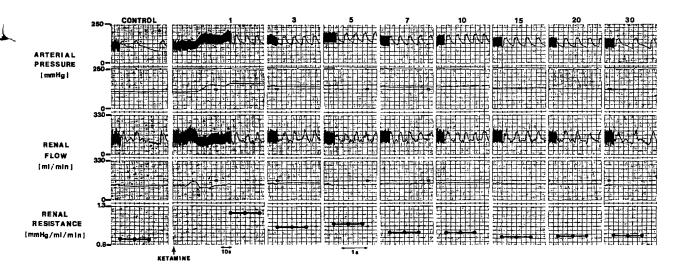
Fig 6. Actual recording of phasic and mean arterial pressure and renal blood flow during control period and after drug injection for a high dose (5 mg/kg) of ketamine. Calculated renal vascular resistance is plotted in bar form in lower panel of this figure. Paper speed is indicated at bottom and can be compared using 1-second tick marks which can be seen between two arterial pressure channels in upper panel.

produced by thiopental (26) or to withdrawal of sympathetic tone (27, 28). Another possibility is that renal vascular autoregulatory mechanisms remain intact after thiopental. In studies on conscious dogs given pentobarbital or thiopental, Burger et al (18) found that renal blood flow decreased 40% to 50%. Another study, however, which examined the effects of pentobarbital on renal hemodynamics in conscious dogs, utilizing techniques identical with the ones used here, showed that renal blood flow did not change after pentobarbital (29). These differences in results may relate to the methodology involved. Burger et al (18) used the microsphere and xenon washout methods, which may have been associated with microsphere clogging of arterioles and background scatter, respectively. In addition, catheters were indwelling in the renal arteries of their animals and the renal arteries had been "cleaned," thereby making disruption of renal innervation a real possibility.

Diazepam as an induction agent has been said to be benign in terms of its cardiovascular depressant properties. Recent studies (30) in patients with coronary disease substantiate this impression. In the present study, neither dose of diazepam significantly decreased arterial pressure. This is consistent with other human and animal studies (4-10) in which only generalized cardiovascular changes were examined. However, renal blood flow was slightly but significantly reduced and renal vascular resistance was increased

by diazepam. Two interesting contrasts can be made between diazepam and thiopental. First, with the high doses, there was an increase in renal blood flow after thiopental but a decrease after diazepam. Second, during the middle-late portion of the observation period, renal vascular resistance decreased after thiopental but increased after diazepam. In both instances, these differences were statistically significantly different (Table). Guignard et al (19) examined the effect of diazepam on RPF in conscious humans and in anesthetized animals as measured by PAH clearance. In patients with prior renal disease, they found that diazepam decreased RPF approximately 26%. In rabbits anesthetized with pentobarbital, however, RPF did not change after diazepam. The PAH clearance technique has limitations. If intrarenal cortical-medullary shunting occurs, the calculated renal plasma flows will be in error (31). The fact that the animals were anesthetized but the patients were not may also explain the difference in results. This emphasizes the importance of studying pharmacologic effects in a system that is not influenced by the simultaneous presence of other drugs.

Ketamine is frequently chosen as an induction agent in situations in which cardiovascular stability is tenuous (32, 33). In many such situations, there is concern for preservation of renal perfusion. Little is known, however, about the effects of ketamine on renal hemodynamics. May it be assumed that, if blood

pressure, heart rate, and cardiac output all increase, as is known to occur after ketamine (13, 34), renal perfusion is maintained? Although not the main mechanism by which ketamine's cardiovascular stimulation is produced, catecholamine levels are elevated after ketamine (35). This could possibly produce renal arterial and arteriolar constriction. We saw the typical increases in arterial pressure and heart rate with both doses of ketamine and can assume from previous studies (13-17) that the cardiac output also increased. It would appear that the kidneys share in the increase in cardiac output following ketamine, as renal blood flow increased significantly by 10% to 15% despite a pronounced increase in renal vascular resistance. The 20% to 40% increases in arterial pressure during the early-middle portion of the observation period represent mean arterial pressure values of 120 to 140 mm Hg, well within the autoregulatory range of the kidney. Thus, the increase in renal blood flow is not due to exceeding the upper limits of autoregulation. The fact that blood flow was increased would lead one to believe that ketamine may be interfering with renal autoregulation. Ketamine has been shown to dilate small arteries in some vascular beds (36). Perhaps this may be occurring in the kidney. Earlier data related to ketamine and renal hemodynamics are not in agreement with our findings. Two studies performed in anesthetized, acutely operated dogs have described a decrease or no change in renal blood flow after ketamine (20, 21). The differences in technique used for measurement of renal blood flow should be considered. The thermoelectric technique utilized by Hirasawa and Yonezawa (20) gives a simultaneous and continual picture of relative renal cortical and medullary blood flows. However, the technique involves placement of needles in the renal parenchyma and the impact of this on renal hemodynamics is unknown. Additionally, the method does not allow for quantitation of flow. The problems associated with the PAH method used by Bevan and Budhu (21) have already been mentioned. A more complete study on the effects of ketamine on cardiac output distribution has been accomplished in conscious rats utilizing a microsphere technique (22). Although the percent distribution of cardiac output going to the kidneys decreased slightly after ketamine, actual renal blood flow, in milliliters per gram per minute, increased by 7% to 20%. These values are similar to our results. Thus it may be anesthetic effects are more important in explaining differences in results than species variations.

Both intravenous and inhalational anesthetics can

so change the picture of renal homeostasis (37) that the validity of pharmacologic studies done in anesthetized systems must be questioned (38, 39). The techniques used in our study obviated the two major problems related to anesthesia and acute surgery. The animals had totally recovered from the surgical experience and were unmedicated and unsedated at the time of the experiments. The control heart rates (Table) are a good indication of their general good health and calm state immediately before administration of the drugs. An additional benefit of our study is that thiopental, diazepam, and ketamine were compared in the same system, thus eliminating differences in results due to experimental design. The methods utilized in the present study are not beyond criticism, however. We did not do simultaneous testing of renal function, i.e., glomerular filtration rate, urine output. The intent was to disturb the homeostasis as little as possible. Additionally, the flow probe technique only measures total flow and does not delineate changes in distribution of blood flow within the organ, i.e., in the kidney, cortical versus medullary blood flow. One can also raise the question of possible vessel denervation with a circumferential probe device. We were careful to use a loose-fitting probe to avoid renal nerve compression and to allow tissue to grow into the probe. The vessel was not cleaned but rather the probe was positioned with a minimal amount of dissection about the vessel. No flow measuring technique is without drawbacks, but we feel this model allows the pharmacologic responses to be studied with minimal disturbance of overall physiology. Certainly, the simultaneous measurement of cardiac output would have been valuable in this study. This was not done because it would have necessitated two operations—a laparotomy plus a thoracotomy. We are currently progressing with a group of animals to examine the simultaneous systemic and pulmonary circulatory picture in response to these drugs.

One other factor to consider is the possibility of changes in arterial blood gases affecting results. Ketamine has minimal effects on arterial Po_2 and Pco_2 (16), yet its hemodynamic changes are immediate. Our previous studies dealing with narcotics have shown that renal hemodynamics are not altered by changes in arterial Po_2 and Pco_2 (40, 41). In our current studies involving systemic-pulmonary changes mentioned above, we have been measuring blood gases because of their effects on the pulmonary system. Thiopental initially decreases Pa_{O_2} some 20 to 30 mm Hg, whereas diazepam decreases it by 10 to 12 mm Hg. Both drugs only increase Pa_{CO_2} 3 to 6 mm Hg.

These effects dissipate by 10 to 15 minutes when Pa_{O_2} and Pa_{CO_2} return to control levels, but the hemodynamic changes persist. Because of the previously demonstrated lack of renal effects with blood gas changes secondary to narcotic administration and the fact that the onset of changes in the kidney precedes the development of the blood gas changes and even outlast the blood gas changes, we believe that our hemodynamic alterations described here are true drug effects and not secondary to blood gas alterations.

In conclusion, using this model we have shown that: (a) generalized, hemodynamic functions may be minimally or significantly altered by a pharmacologic agent at a time when important hemodynamic changes are occurring in the kidney; (b) there are important differences that exist between thiopental, diazepam, and ketamine in their effects on renal hemodynamics and these do not appear to be dose related for these drugs; and (c) hemodynamic studies of anesthetic drugs performed in anesthetized animals may differ markedly from studies in conscious animals.

ACKNOWLEDGMENTS

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Transcutaneous Cranial Electrical Stimulation Decreases Narcotic Requirements during Neurolept Anesthesia and Operation in Man

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STANLEY, T. H., CAZALAA, J. A., ATINAULT, A., COEYTAUX, R., LIMOGE, A., AND LOUVILLE, Y.: Transcutaneous cranial electrical stimulation decreases narcotic requirements during neurolept anesthesia and operation in man. Anesth Analg 1982;61:863-6.

The influence of transcutaneous cranial electrical stimulation (TCES) on fentanyl requirements was evaluated in 50 patients undergoing urologic operations with pure neuroleptanesthesia (droperidol, diazepam, fentanyl, and air-oxygen) with (group I) or without (group II) simultaneous TCES. All patients had silver electrodes (three) applied between the eyebrows and behind each mastoid process and attached to a 167-kHz current generator. Current was delivered only to group I. The wave form was a complex nonsinusoidal, nonsquare wave pattern which was applied intermittently in a 3-msec-on 10-msec-off sequence. All patients had anesthesia induced with droperidol (0.20 mg/kg IV), diazepam (0.2 mg/kg IV), and pancuronium (0.08 mg/kg IV), and, after tracheal intubation, had anesthesia maintained with fentanyl in 100-μg intravenous increments every 3 minutes whenever and as long as systolic arterial blood pressure and/or heart rate were >20% of control (preanesthetic induction) values. Fentanyl requirements averaged 6.1 ± 0.5 and 7.9 ± 0.4 μg/kg/min for a mean total dosage of 9.0 ± 0.9 and 12.5 ± 0.8 μg/kg for the entire operation in groups I and II, respectively. These differences between groups were statistically significant ($p <$ 0.05). The data demonstrate that TCES augments the analgesic effects of fentanyl and thus reduces fentanyl requirements during urologic operations with neuroleptanesthesia.

Key Words: NERVE: stimulator, transcutaneous cranial electrical.

TRANSCUTANEOUS electrical stimulation (TENS) is successfully being used to treat some patients with chronic pain (1-3). There are also data from a number of investigators that indicate that TENS is an effective method of minimizing acute postoperative pain (4-7). A special form of TENS, transcutaneous cranial electrical stimulation (TCES), in which stimulating electrodes are placed on specific areas of the head, is being used with increasing frequency as a supplement to N_2O-neuroleptanesthesia in France and many other countries in Europe (8, 9). In a recent study (10), we demonstrated that TCES significantly increases the potency of N_2O in unpremedicated patients before surgery. This suggests that simultaneous use of TCES during clinical anesthesia might decrease patient requirements for inhalation or intravenous anesthetics. In this study we evaluated the influence of TCES on fentanyl requirements in 50 adult patients undergoing suprapubic and retropubic prostatectomies with pure neuroleptanesthesia (droperidol, diazepam, fentanyl, and air-oxygen) with (group I) or without (group II) simultaneous TCES.

Methods

The protocol was approved by the Necker Hospital Human Experimentation Committee. Informed consent was obtained from each patient at the time of the preoperative visit.

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The patients were premedicated with atropine (0.1 mg/15 kg IM) and diazepam (1.2 mg/10 kg IM) 60 minutes before scheduled arrival in the operating room and randomly assigned to groups I and II. Patients were not informed as to which group they were assigned. Patients selected for inclusion in the study were A.S.A. class I or II and without significant cardiac, pulmonary, hepatic, or central nervous system dysfunction. Some patients had urinary obstructive disease, but none had a serum blood urea nitrogen level greater than 50 mg/100 ml.

Upon arrival in the operating room, the patient was given an intravenous infusion of dextrose 5% in water in an arm vein, a bipolar lead II electrocardiogram was continuously recorded (and used to determine heart rate), and a standard blood pressure cuff was applied to an upper arm before the study began. Then TCES-stimulating electrodes were applied to the head in all patients and their wire connections attached to the current generator. (This was done in all patients although only half of the patients had the current turned on.)

The electrical stimulus was generated by a high-frequency (167 k Hz) generator. The wave form was a complex nonsinusoidal, biphasic nonsquare wave pattern (Figure) which was applied intermittently in a 3-msec-on and 10-msec-off sequence. The peak-to-peak intensity ranged between 250 to 300 mA (depending on patient skin resistance), but because of the biphasic nature of the wave, average intensity was 0 mamp. (Our pulse generator is designed to produce a wave form composed of one positive impulse of high intensity and short duration followed by one negative impulse of low intensity and long duration.
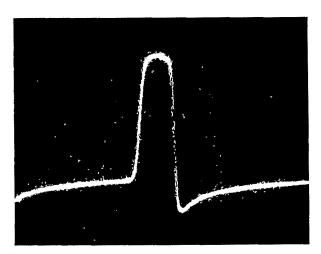
FIGURE. Wave form of electrical stimulus used to produce transcutaneous cranial electrical stimulation.

As a result, average pulse intensity is 0 mamp.) Current was delivered to the patients' cranial skin via three silver (paste-on) electrodes of 13.3 mm^2 area. The electrodes were applied between the eyebrows and one each over or slightly posterior to each mastoid process, depending on the patient's natural hair line.

Two anesthesiologists were responsible for anesthesia in all patients. Both anesthetized equal numbers of patients in groups I and II. The anesthetists were blinded as to which patients were to receive TCES. Before induction, the TCES current was turned on in patients in group I by another investigator (not an anesthesiologist), who monitored the current generator throughout the duration of anesthesia. He positioned and covered the generator screen so that it was impossible for the anesthesiologist to determine whether TCES current was flowing. (Patients cannot tell whether or when the TCES current is turned on as it does not produce any detectable sensation.)

All patients were given oxygen to breathe and had anesthesia induced with droperidol (0.15 mg/kg IV), diazepam (0.2 mg/kg IV), and pancuronium (0.08 mg/kg IV). Three minutes after administration of pancuronium, their tracheas were intubated with a Portex endotracheal tube and respirations controlled with 40% oxygen and 60% nitrogen at rates (10 to 15 breaths/min) and tidal volumes (10 to 12 ml/kg) necessary to maintain Pa_{CO_2}, as continuously estimated via end-tidal CO_2 analysis, at 37 to 43 torr. Anesthesia was maintained with 100-μg increments of intravenous fentanyl. Fentanyl was given every 3 minutes whenever and as long as systolic arterial blood pressure and/or heart rate were 20% or more above control (preanesthetic induction) values or if patients demonstrated other evidence of light anesthesia, e.g., sweating, cutaneous flushing. Systolic arterial blood pressure and heart rate were measured every 5 minutes throughout anesthesia and surgery except when either variable was 20% or more above control values at which times they were measured every minute. Muscle relaxation was maintained with pancuronium (1 to 2 mg IV) every 45 to 60 minutes throughout surgery. At the end of surgery, muscle relaxation was reversed with atropine (2.0 mg IV) and neostigmine (5.0 mg IV), and TCES was discontinued (group I). When respiratory rate was greater than 8 breaths per minute and tidal volume >5 ml/kg (as measured via a Wright spirometer in the exahalation limb of the circle system) patients were extubated. Patients were interviewed 24 hours after surgery and questioned about memories of the anesthetic and surgical procedures.

Results

The ages (68 ± 8, mean ± SD), weights (72 ± 12 kg), preoperative heart rates (80 ± 8 beats/min), systolic arterial blood pressures (122 ± 11 torr), and operative times (123 ± 34 min) were similar in the two groups. These values were analyzed using Student's unpaired t-test. None of the patients were taking diuretics, digitalis preparations, beta-adrenergic blocking drugs, calcium blocking drugs, vasodilators, or other cardiac medications before surgery.

Fentanyl requirements averaged 6.1 ± 0.5 and 7.9 ± 0.4 μg/kg/min for mean total dosages of 9.0 ± 0.9 and 12.5 ± 0.8 μg/kg for the entire operation in group I and II, respectively. Differences in fentanyl dosage between the two groups were statistically significant ($p < 0.005$). All patients were responsive to command and spontaneously breathing at rates of 12 breaths per minute or greater within 15 minutes of the end of surgery. No patient required a narcotic antagonist. When interviewed 24 hours after surgery, no patient remembered any aspect of tracheal intubation, or the anesthetic or surgical procedures.

Discussion

The results of this study demonstrate that transcutaneous cranial electrical stimulation significantly increases analgesia during neuroleptanesthesia and thus reduces fentanyl requirements during urologic operations. Analgesia with TCES appears to be achieved without harmful effects to the patients and without increases in the duration of postoperative respiratory or central nervous system depression.

In a recent study (10) we demonstrated that TCES potentiates both the analgesic and amnesic actions of N_2O and thus deepens anesthesia with N_2O in man. The mechanism by which TCES produces increased analgesia and amnesia with N_2O and increased analgesia during neuroleptanesthesia with droperidol, diazepam, and fentanyl is unknown. Volunteers having TCES without N_2O for 1 hour are not sleepy or amnesic, but 40% of them report a warm and tingling sensation all over their bodies and 70% are objectively analgesic to many forms of painful stimulation (T. H. Stanley, A. Limoge, unpublished data, 1980). Similar results have been obtained with some TENS units in patients with chronic pain (4–7). It has been suggested

that TENS units may stimulate certain receptor sites situated in the spinal cord, in the central gray area of the brain, and perhaps other areas of the central nervous system which regulate the perception of somatic pain and/or produce analgesia (11). Direct electrical stimulation of these receptor sites has been shown to result in pain relief which can be antagonized by narcotic antagonists (12, 13). Whether TCES stimulates central nervous system opiate receptors directly, indirectly (via stimulation of cutaneous nerves with secondary transmission of impulses up the spinal cord to the brain), or at all is unknown. In patients subjected to craniotomy with TCES, droperidol, fentanyl, and N_2O anesthesia, it has been possible to measure changes in electrical potential within cerebral cortical tissue when TCES current is applied (A. Limoge, unpublished data, 1979). It is unknown, at this time, whether similar electrical potential changes occur in other areas of the brain (i.e., the central grey area where high concentrations of opiate receptors are known to exist) and if so, whether such changes are effective in stimulating opiate receptors.

There are data that demonstrate that the analgesic actions of TENS can be reversed with antagonists such as naloxone (14). TCES also produces analgesia in patients with chronic pain which can be antagonized by naloxone (A. Limoge, unpublished data, 1979). This suggests that TENS and TCES may be producing analgesia by stimulating increased production and/or release of endogenous analgesics, the endorphins, enkephalins, and/or other neurotransmitters. Whether this is in fact true, has, at least to our knowledge, not yet been documented in man.

It is clear from this investigation, from our previous study with N_2O, and from our unpublished observations in unanaesthetized volunteers that TCES provides some analgesia and perhaps some amnesia but not enough by itself to be used as an anesthetic. Whether TCES or any form of TENS provides advantages when used during anesthesia has not yet been documented. Theoretically, lower doses of narcotics or lower concentrations of inhalation anesthestics should result in less major organ system alterations in function during anesthesia. This could mean that anesthesia with TCES produces less physiologic insult than more standard anesthetic techniques and results in a shorter postoperative recovery period. In our previous study (10), we found that analgesia after TCES lasted into the early postanesthetic recovery period, after N_2O was gone. This suggests that intraoperative use of TCES might reduce postanesthetic analgesic requirements. Unfortunately, many more

Data were analyzed for statistical significance using Student's unpaired t-test and the chi-square test; $p < 0.05$ was considered statistically significant.

carefully performed studies are needed before any of these or other theoretical advantages of TCES can be confirmed.

In conclusion, the results of this study demonstrate that transcutaneous cranial electrical stimulation (TCES) significantly increases the degree of analgesia achieved during neuroleptanesthesia for urologic operations and thus reduces intraoperative fentanyl requirements. These findings suggest that simultaneous use of TCES and neuroleptic compounds during neuroleptanesthesia may provide advantages when compared with using neuroleptic compounds by themselves.

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Emergency Percutaneous Transtracheal Ventilation during Anesthesia Using Readily Available Equipment

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Percutaneous transtracheal ventilation has been described as a possible technique for use during anesthesia in the management of acute upper airway obstruction. This study describes a modified percutaneous transtracheal ventilation device for use with standard anesthesia machines. Unlike previously reported devices, this device does not require specialized equipment or prior assembly. The efficacy of this device was tested on anesthetized dogs. Adequate ventilation was easily maintained as documented by serial arterial blood gas determinations, and the device also proved capable of reversing severe hypercapnea such as might result from upper airway obstruction. Extrapolation of the data obtained from these experiments indicates that this device, if used properly, should provide adequate ventilation and oxygenation in adult humans.

Key Words: VENTILATION: transtracheal.

Percutaneous transtracheal ventilation (PTV) was

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first described approximately 10 years ago (1, 2). Since that time, there have been numerous reports of the use of this technique both during anesthesia (1, 3, 4) and as an alternate means of ventilatory support during acute upper airway obstruction (5–10). This technique, if used properly, provides adequate ventilation and oxygenation with low morbidity and mortality.

A careful preoperative evaluation will usually uncover upper airway abnormalities that would make intubation difficult. This allows time for planning and preparation of optional intubation equipment. Occasionally, however, a situation may arise in which unanticipated airway obstruction occurs acutely. All previously reported devices for delivering PTV require prior assembly of customized regulators, special tubing, or connectors with or without toggle or pushbutton pneumatic valves coupled to special high-pressure oxygen or air sources (1–10). If conventional techniques fail to establish an airway, little time may be left to locate this specialized equipment. We describe a modified PTV device that can be assembled rapidly from parts found on virtually any anesthesia machine, and we also report results documenting adequate ventilation with this device in an animal model.

Description of Device

To assemble the device, the fresh gas hose from the anesthesia machine is disconnected from the CO_2 absorber-circle system and connected to a length of standard oxygen tubing (e.g., #115 Hudson Oxygen Therapy Sales, Temecula, CA) with a double-end connector (e.g., #360, Pharmaseal, Inc., Toa Alta, PR) (see Fig 1). The trachea is then cannulated through the cricothyroid membrane using a 14-gauge, 5-cm plastic over the needle intravenous catheter (e.g., #2812 Deseret, Sandy, UT). A syringe attached to the intravenous catheter permits constant aspiration while the tracheal puncture is performed; air aspiration provides confirmation that the catheter is within the lumen of the trachea. The catheter is advanced toward

Fig 1. Individual parts of PTV device: A, Angiocath 14-gauge; B, three-way plastic stopcock; C, oxygen tubing; D, double end connector; E, fresh gas hose from anesthesia machine.
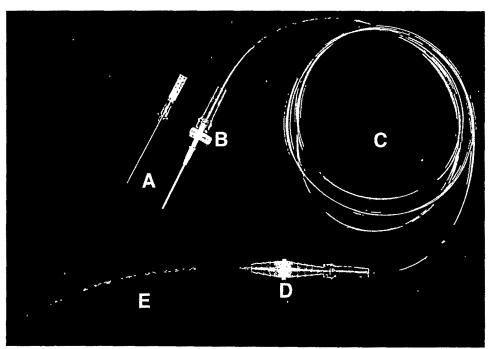
the carina after the needle has been removed. The intratracheal position is again confirmed by aspiration and injection of air. A three-way plastic stopcock (e.g., model #75, Pharmaseal) is placed between the oxygen tubing and the hub of the 14-gauge crico-thyroid catheter to serve as a connector. The male end of the stopcock fits into the hub of catheter. The oxygen tubing will fit tightly over the female end of the stopcock, thus providing a readily available adapter for securing oxygen tubing to catheter. Ventilation with 100% oxygen is accomplished by intermittently activating the flush system on the anesthesia machine while holding the catheter in place by hand. Exhalation occurs passively through the larynx when the oxygen flush valve is released. The effectiveness of this device was tested in apneic dogs and is reported below.

Methods

Four mongrel dogs (20 to 23 kg each) were anesthetized with sodium pentobarbital (15 mg/kg IV) and, following tracheal intubation, paralyzed with pancuronium (0.1 mg/kg) with respiration in the supine position maintained using a Harvard ventilator before the onset of the experiment. Tidal volumes of 15 ml/kg were delivered at a rate adjusted to maintain Pa_{CO_2} between 35 and 45 torr. The femoral artery was cannulated to permit monitoring of blood pressure

and heart rate, and sampling of arterial blood. Tidal volume was measured indirectly with a Manning pneumograph. A 14-gauge, 13-cm catheter was then inserted percutaneously through the cricothyroid membrane and advanced distally in the trachea to the level of the carina. Airway pressures were measured through this catheter with a Statham transducer (model #P23PD) and recorded on a Grass model 7 polygraph. Arterial blood gas tensions were measured using an IL model 213 machine. The experimental protocol was divided into two parts.

Part I

After adjusting ventilation to within the above mentioned limits, the trachea was extubated. An additional 14-gauge, 5-cm catheter was then inserted into the trachea as described under "Description of Device" and percutaneous transtracheal ventilation was begun. An attempt was made to provide uniform ventilation (rate approximately 8 breaths/min, tidal volume approximately 400 ml) by observing the polygraph tracing. Arterial blood samples were drawn serially at 5-minute intervals during the next 30 minutes. Ventilation was adjusted based on blood gas tension measurements.

On two occasions during the 30 minutes of percutaneous transtracheal ventilation, a 10-second period of sustained insufflation was performed by maintain-

ing a constant O_2 "flush" through the PTV catheter to determine the maximum airway pressure and maximum tidal volume that could be delivered with this device.

Part II

To assess the ability of the device to reverse rapidly severe hypercapnia, each animal was allowed to remain apneic to permit respiratory acidosis to develop. Oxygenation was maintained during apnea by delivering oxygen through the PTV catheter at 2 L/min. When the Pa_{CO_2} reached approximately 100 torr, PTV was started with tidal volumes of approximately 400 to 500 ml delivered at the maximum rate obtainable. Serial arterial blood gas tensions were measured.

After 20 minutes, PTV was discontinued, the trachea was reintubated, and the animals were ventilated until they recovered sufficiently from the anesthetic to permit extubation.

Results

Part I

During 30 minutes of percutaneous transtracheal ventilation, tidal volumes of 438 ± 140 ml (mean ± SEM) were delivered at a frequency of 8.5 ± 0.3 breaths per minute. Throughout this period normocarbia was maintained and hypoxia was avoided (see Fig 2). Pressure generated in the upper airway during PTV was 12 ± 1.2 cm H_2O.

Blood pressure and heart rate remained at base line levels throughout the 30-minute test period. The maximum airway pressure that could be generated by this device under these experimental conditions was 28 ± 1.4 cm H_2O which resulted in a tidal volume of 838 ± 140 ml. Mean blood pressure declined approximately 15 to 20 mm Hg when maximum airway
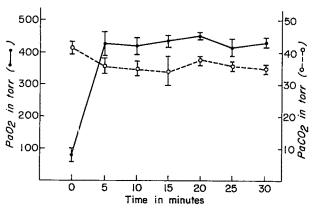
Fig 3. Arterial oxygen and carbon dioxide tensions after apneic oxygenation followed by 20 minutes of PTV (mean ± SEM).
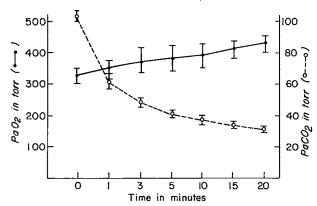
pressures were recorded but rapidly returned to base line during passive exhalation.

Part II

Ventilation with the PTV device rapidly reversed hypercapnia produced during apneic oxygenation. Normocarbia was obtained within 4 minutes (see Fig 3). Arterial oxygenation was well maintained by low-flow oxygenation during the period of apnea (Pa_{O_2} > 400 torr). Heart rate and blood pressure did not increase either during apneic oxygenation or during the period of hyperventilation which followed. The maximum ventilatory rate that could be sustained was 17.3 ± 1.1 breaths per minute with a tidal volume of 457 ± 41 ml.

Discussion

Percutaneous transtracheal ventilation has been the subject of many reports demonstrating a number of different devices for successful use during both anesthesia (1, 3, 4) and emergency airway management (5–10). All the devices previously reported, however, require prior assembly and/or purchase of special articles of equipment. During anesthesia for patients with suspected upper airway abnormalities, it is possible to have specialized equipment available. However, where an unsuspected airway management problem arises that cannot be solved by conventional techniques, there may not be time to send for commercial PTV devices which are often stored in a central location within the operating room. As suggested by DeLisser and Muravchick (9), ideally an optional PTV system should be made available and kept on each anesthesia machine. However, in lieu of this, the PTV device described in this report may be quickly assembled from readily available items.

Fig 2. Arterial oxygen and carbon dioxide tensions during 30 minutes of PTV (mean ± SEM).
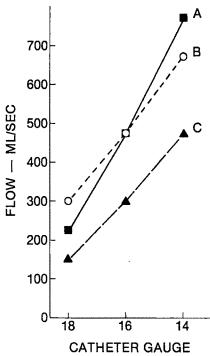
FIG 4. Flow rates through PTV device using different size catheters and different anesthesia machines: A, Ohio Kinet-O-Meter; B, Ohio Modulus; C, Foregger Foretrend 300.

Proper functioning of any PTV device requires that adequate flow rates be delivered through the catheter. The data herein described were obtained using an Ohio Kinet-O-Meter anesthesia machine, which generated flows of approximately 800 ml/sec through the PTV device. Flow rates through different sizes of catheters using various anesthesia machines are shown in Fig 4. In some cases, adequate flow rates and hence adequate ventilation might be maintained through a smaller cricothyroid catheter. However, because of the variability of flow rates generated by different anesthesia machines, we recommend use of 14-gauge catheters for PTV in adult patients.

The data presented here demonstrate that our device can provide more than adequate ventilation and oxygenation for prolonged periods of time in dogs. Projecting these results to an adult human, we predict that adequate minute ventilation could be delivered. Total pulmonary compliance is affected by numerous factors including lung volume, posture, age, and anesthesia. In anesthetized, paralyzed human subjects, total compliance ranges from approximately 60 ml/cm H_2O (dynamic) to 85 ml/cm H_2O (static) (11). The upper airway pressures generated by our PTV device should provide adequate tidal volumes without exceeding safe upper airway pressures (12).

Safe use of PTV with any device requires a patent

larynx to permit passive exhalation. In patients in whom laryngospasm or total upper airway obstruction is present, this device may be used for low-flow apneic oxygenation by reducing the flow of oxygen from the anesthesia machine. This would allow time for more definitive measures, such as tracheostomy, while adequate oxygenation is maintained. Hypercapnia that develops during apneic oxygenation has been shown to be well tolerated if hypoxemia is avoided (13). Reported complications with various PTV devices are usually minor; however, the possibility of serious complications does exist (14). During this experiment no immediate difficulties were encountered, and all dogs had uneventful recovery from anesthesia. There were no complications noted during the week following the experiment.

The PTV device presented here is a simple and safe method for treating unexpected upper airway obstruction in the operating room when conventional techniques fail. The device provided more than adequate oxygenation and ventilation in the experimental model tested. Although we do not recommend that this PTV device be used in place of standard airway management techniques, in selected cases its use might prevent asphyxiation when conventional methods of airway management fail.

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CLINICAL reports

A Gravity-Driven Continuous Flush System for Vascular Catheters

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The use of indwelling vascular catheters for continuous monitoring of arterial blood pressure and cardiac filling pressures is commonplace in the operating room and intensive care unit. Complications of intra-arterial cannulation include arterial thrombosis, ischemia of distal areas of the extremity, skin necrosis, and aneurysm formation (1-3).

To decrease the risk of thrombosis, the continuous infusion of heparinized solution into the cannulated vessel at low rates (1 to 3 ml/hr) is standard practice. Two methods of continuous infusion are currently utilized: (a) electrical infusion pumps, and (b) intravascular infusion of flush solution under high pressure (300 torr) metered through a small capillary tube. The continuous flush device also permits rapid flushing to purge the pressure monitoring line of blood and air. The usual source of high pressure flush solution used in conjunction with the continuous flush device is a 250-ml plastic bag of heparinized solution pressurized to 300 torr with an inflatable blood pump. Specific hazards of this high pressure system are the rapid infusion of large volumes of solution or air if the metering device fails, and an inability to monitor accurately the volume of solution infused. Furthermore, a leak in the blood pump will cause a loss of pressure with subsequent retrograde

flow of blood into the pressure monitoring line and transducer. These flush devices can also result in a false elevation of the monitored pressure (4). These hazards are of considerable significance in the infant and small child. To obviate the hazards of the currently used pressurized system we have constructed a gravity-driven source of high pressure flush solution.

Description of System

The device consists of a 2.7-kg cylindrical weight housed within a section of 37-mm diameter polyvinylchloride pipe. The weight is applied to the plunger of a 50-ml calibrated plastic syringe that has been inserted into one end of the pipe (Figure). The weight has a handle that protrudes through a "J"-shaped slot in the pipe which permits the user to remove the weight from the syringe plunger when refilling the syringe or before insertion of the vascular cannula. The mass of the cylindrical weight was chosen to produce a pressure of 300 torr in the syringe. A pressure of 50 torr is required to overcome the frictional resistance of the syringe plunger in the barrel. The weight therefore generates the equivalent of 350 torr over the cross-sectional area of the syringe plunger. The polyvinylchloride housing is suspended from an intravenous bottle stand. The syringe is connected to the continuous flush device with a 20-cm intravenous extension tube.

The total volume of flush administered can easily be monitored by visual inspection of the volume change on the 50-ml syringe barrel. The volume of flush given during a rapid flush can likewise be controlled by observing the movement of the syringe plunger and releasing the rapid flush valve as soon as the desired volume of flush solution has been administered. We have used this device for more than 1000 vascular catheters without complication. The only problem has been the occasional finding of a syringe with a very tight fit between the barrel and the
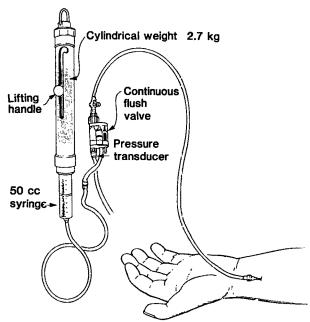
FIGURE. Gravity-driven continuous flush system. Stippled area represents weight that is housed within pipe.

plunger. This problem is recognized by the failure of the syringe plunger to move during a rapid flush.

Discussion

Because the use of indwelling vascular catheters as perioperative monitors has become routine practice, it is imperative that the complications of these invasive monitors be minimized. Continuous flushing is considered essential to maintain the patency of both the cannula and the vessel. Besides the hazards of vascular cannulation there are also hazards of the currently used high pressure flush systems. The air-inflated blood pump may leak; with loss of the pressure head blood can leak back into the catheter and pressure monitoring line. If the catheter becomes occluded, it must be removed. It is also possible, by the excessive use of the rapid flush feature, to infuse a large volume of flush solution as there is no way to monitor precisely the volume of flush solution administered. We have encountered some continuous flush devices in which the flush valve has become lodged in the open position, resulting in rapid solution administration. There is also a potential risk of air embolization from air bubbles pressurized into the flush solution. This risk is greatest when microdrip chambers are used to connect the pressurized bag to the continuous flush device (5). The electrical infusion pumps are of two types. The electrical pumps which utilize a high-volume fluid reservoir have the same hazards as the pneumatic systems. The electrical syringe pumps, although expensive, do provide an accurate method of monitoring volume infusion.

Our gravity-driven device eliminates many of the hazards of the pneumatic-powered devices such as overinfusion and air embolization. The gravity device is simple to use, inexpensive to construct, and requires no electrical or pneumatic power source. It is especially suited for use in the infant and small child. It can be used for arterial, central venous, and pulmonary arterial catheters.

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Ketamine and Myoclonic Encephalopathy of Infants (Kinsbourne Syndrome)

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Anesthesiologists are frequently called on to provide assistance for diagnostic procedures in young, uncooperative children. In many such situations, painful stimulation is minimal and the requirement for immobility is brief. Ketamine hydrochloride, intramuscularly or intravenously, has often been recommended for such procedures (1-3). We used this agent in a child with myoclonic encephalopathy of infants and encountered an unexpected complication. We describe our experience and discuss the anesthetic considerations for this rare condition.

Case Report

A 12-month-old, 9.3-kg male infant was admitted to Children's Hospital for observation and evaluation of opsoclonus, myoclonus, and ataxia. The child was the product of a full-term, uncomplicated pregnancy in a 25-year-old primigravida. Labor began spontaneously and lasted 17 hours; the child was delivered with the aid of spinal anesthesia and outlet forceps without complication. Apgar scores were 7 at 1 minute and 8 at 5 minutes. Past medical history was unremarkable and developmental milestones were normal. Two days before admission, he spontaneously developed opsoclonus, characterized by chaotic eye movements, and myoclonus involving all four extremities, usually one extremity at a time. His gait and balance became unsteady and he reverted to crawling from walking.

Neurologic examination on admission revealed chaotic, conjugate, and jerking eye movements. Motor examination revealed asymmetrical, fast jerking movements of all extremities as well as truncal instability on sitting. Terminal dysmetria was present when reaching for objects and a

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positive Babinski was present bilaterally. Laboratory studies including cerebral computed tomography (CT), electroencephalography (EEG), and cerebral spinal fluid (CSF) analysis were within normal limits. Findings from serum protein electrophoresis were normal, and viral cultures were negative.

The clinical diagnosis at this time was myoclonic encephalopathy of infants. Because this syndrome may be associated with an occult neoplasm (4) a work-up for neuroblastoma was initiated. Although urine vanillylmandelic acid values were normal, abdominal CT scan showed a mass extending from the kidney to the vertebral column.

Exploratory laparotomy was performed. The anesthetic technique consisted of a narcotic (morphine sulfate) relaxant (pancuronium bromide) sequence with nitrous oxide in oxygen. All visible tumor was removed. Frozen section at the time of surgery showed margins free of tumor. Pathologic review revealed islands of neuroblastoma surrounded by stroma of a ganglioneuroma with neurofibromatous changes at the edge of the surgical specimen. Anesthesia and surgery were uncomplicated.

Eight days after surgery, a myelogram was scheduled to assess possible spinal cord involvement. The patient's condition was unchanged with persistent myoclonus, opsoclonus, and ataxia. No oral feedings were given for 6 hours before induction of anesthesia; atropine, 0.1 mg, was administered intramuscularly 45 minutes before the myelogram was performed. Blood pressure, respirations, and electrocardiogram were monitored. Anesthesia was induced with an intramuscular injection of ketamine hydrochloride, 50 mg. Over the next 3 minutes myoclonus and opsoclonus increased in severity. An intravenous catheter was inserted and additional ketamine, 10 mg, was administered intravenously, but the severe myoclonus and opsoclonus persisted. As the procedure could not be performed because of the continued movement, sodium thiopental, 10 mg, was administered intravenously. Abnormal movements ceased immediately. The patient was than positioned and the myelogram was performed without further difficulty or additional anesthesia. During recovery, myoclonus and opsoclonus reappeared.

The myelogram findings were normal. The child was felt to have stage I-II neuroblastoma and additional therapy was deemed unnecessary. Four months later the child still exhibited the clinical features of the myoclonic encephalopathy of infants with mild spontaneous improvement.

Discussion

Myoclonic encephalopathy of infants (MEI), also known as the "dancing eyes, dancing feet" syndrome or the Kinsbourne syndrome, was first described by Kinsbourne in 1962 (5). The syndrome consists of a triad of cerebellar ataxia, opsoclonus (irregular eye movements in the horizontal and vertical planes), and

myoclonus (irregular jerking of the muscles of the trunk and limbs). Laboratory findings including EEG are typically normal (4-6), but no studies utilizing deep electrode implantation have been carried out. As the surface EEG represents only a small fraction of the electrical activity deep in the brain, it is possible that deep ongoing seizure activity may be producing the clinical picture of MEI.

MEI is a rare syndrome; fewer than 100 cases have been reported in the literature (4). MEI is known to occur in two situations: 54% of cases follow an infectious episode (primarily respiratory or gastrointestinal); 46% are associated with a neuroblastoma (4). The etiology of MEI is unclear. Because of the clinical manifestations, cerebellar and brainstem structures would be expected to be involved, but laboratory and postmortem pathologic studies have failed to demonstrate any abnormalities in these areas. Clinical improvement with steroid therapy and/or tumor removal suggests some form of immunologic involvement (7).

The wisdom of using ketamine in children with this disorder can be questioned. The administration of ketamine produces a cataleptic state characterized by the presence of nystagmus. Purposeful movements unrelated to surgical stimulation may be present (8) as may increases in muscle tone (9), generalized extensor spasms (10), and purposeless movements (1, 2, 3, 11) that may interfere with surgical or diagnostic procedures (3). It has been suggested that the abnormal muscle movements reflect increased activity in the limbic and thalamic regions despite a normal surface EEG (11).

The ability of ketamine to increase electrical activity in the neocortex, hippocampus, and other subcortical regions while leaving cortical regions unaffected was first demonstrated in cats by depth electrode monitoring (12). Clinically, depth electrode recordings in adult patients with severe epilepsy showed a consistent increase in limbic and temporal electrical activity, after the administration of ketamine, without corresponding increases in electrical activity in surface EEG patterns (11).

In children, surface EEG patterns after ketamine administration are the same as those demonstrated in adults (13). In both children and adults, surface EEG electrical abnormalities suggestive of increased subcortical (epileptiform) activity have been reported. In these cases, this activity increased after the administration of ketamine (13, 14).

The clinical manifestations of MEI may result from a lesion involving subcortical areas of brain not re-

flected by surface EEG patterns. The administration of ketamine could further stimulate these areas with a result increase in myoclonus and opsoclonus as we observed.

What was surprising was the small dose of sodium thiopental that was required to abolish the abnormal movements. The requirement of such small doses has been previously noted by Radnay and Badola (10), who used small doses of pentobarbital sodium, 2 mg/kg, to treat generalized extensor spasm occurring during recovery from ketamine anesthesia for minor surgery. Our case is different in that pathology was present before the administration of ketamine. All clinical symptoms were abolished with the administration of thiopental, implying the presence of an irritable focus; the activity of such a focus would be expected to be abolished by a central nervous system depressant (11) as we observed.

A second reason for avoiding ketamine in children with MEI is the high incidence of neuroendocrine tumors in this condition (4). Ketamine may result in catecholamine release with consequent elevations in heart rate and blood pressure and tachyarrhythmias as was reported in patients with pheochromocytoma (15).

In summary, we feel that in children with MEI ketamine should be avoided because it may potentiate myoclonus and opsoclonus and because it may cause further sympathetic stimulation in patients with neuroendocrine tumors.

If anesthesia is required for major surgery, we feel that a technique appropriate for a patient with a neuroendocrine tumor, such as a nitrous oxide in oxygen, narcotic, relaxant technique, or a technique utilizing enflurane, be utilized (15, 16). For procedures involving minimal stimulation, such as CT scan, myelogram, or radiotherapy, intravenous, intramuscular or, rectal barbiturates may provide sufficient sedation (or anesthesia) for performing the procedure (1).

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Cannulation of the Dorsal Radial Artery: A New Technique

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Percutaneous cannulation of the radial artery is commonly performed to monitor arterial blood pressure and obtain arterial blood samples for blood gas analysis. The radial artery is usually entered on the volar aspect of the wrist. It is also possible to cannulate the radial artery on the dorsum of the hand, where it emerges from the anatomic snuffbox. Here the radial artery assumes a superficial location, passing beneath the tendon of the extensor pollicis longus and between the bases of the first and second metacarpals. This report reviews our experience with dorsal radial arterial cannulation.

Methods

Dorsal cannulation of the radial artery, as it emerges from the anatomic snuffbox, was attempted in 45 consecutive patients undergoing elective vascular reconstructive procedures. An Allen's test (1) was performed to confirm the presence of a patent ulnar collateral blood supply to the hand. The location of the radial artery was determined by palpation of the pulse on the dorsum of the hand between the bases of the first and second metacarpals. The skin was prepared with povidone-iodine solution, and after raising a skin wheal with 1% lidocaine, a 20-gauge Teflon catheter was inserted percutaneously. When

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a brisk blood return was obtained, the catheter was advanced to the hub, a distance of 2.8 cm. Once in place, the catheter was continuously flushed with a heparin solution, connected to an arterial transducer, and secured. The hand was immobilized in the position of function. Daily evaluations of the hand were performed while the catheters were in place and again 48 hours following removal.

Results

Successful cannulation of the dorsal radial artery was achieved in 35 of the 45 patients. Although successful radial arterial cannulation was accomplished in 78% of the patients in this series, more than one pass was required in 11 patients before satisfactory catheter placement was achieved. When the dorsal radial artery could not be cannulated, the catheter was then inserted into the radial artery on the volar surface of the wrist.

The mean duration of dorsal radial arterial cannulation was 39 hours (range 1 to 120 hours). There were no instances of digital ischemia, pain, or paresthesias in the hand following removal of the catheter. All patients continued to have a palpable volar radial pulse and an intact superficial palmar arch by clinical evaluation.

Discussion

Digital ischemia with loss of tissue is a grave complication of radial arterial cannulation. This complication has been attributed by many authors (2–5) to thrombosis of the volar radial artery at the site of catheter insertion with embolization to the superficial palmar arch. Many factors have been shown to increase the frequency of radial arterial occlusion (6, 7). Both catheter size and type of catheter material influence the incidence of arterial occlusion. The use of 18-gauge catheters is associated with a greater likelihood of thrombosis than the use of 20-gauge catheters. Similarly, polypropylene catheters cause arterial occlusion more frequently than do Teflon catheters. Other factors that promote development of radial arterial occlusion include duration of cannulation, arterial cut-down, multiple arterial punctures, development of hematoma, hypothermia, and low cardiac output.

The digital arteries that supply the fingers arise from the superficial palmar arch. The latter is formed from the anastomosis of the palmar branch of the radial artery with the ulnar artery. The radial arterial contribution to the superficial palmar arch, the palmar

branch of the radial artery, arises from the main radial artery on the volar surface of the wrist before the latter enters the anatomic snuffbox (Fig 1). It should prove advantageous to cannulate the radial artery on the dorsum of the hand as it emerges from the snuffbox because this site is distal to the origin of the palmar branch of the radial artery. Sparing this important collateral vessel should, therefore, further decrease the incidence of digital ischemia. In contrast, when the radial artery is cannulated on the volar aspect of the wrist, any thrombus that develops will occlude the radial contribution to the superficial palmar arch. The palmar branch of the radial artery also provides important vasculature to the thumb (8).

The volar aspect of the wrist is a popular site for arterial catheter insertion because of the superficial position of the radial artery in this location. It is important to note that the radial artery on the dorsum of the hand also occupies a superficial position as it emerges from the anatomic snuffbox. The dorsal radial artery passes beneath the tendon of the extensor

FIG 2. Cadaver dissection showing dorsal radial artery (a) emerging from anatomic snuffbox, passing beneath tendon to extensor pollicis longus (b). Note proximity of cephalic vein (c).
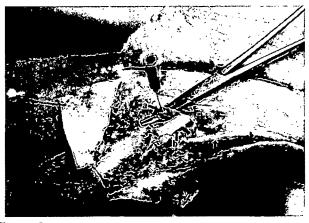
pollicis longus and between the bases of the first and second metacarpals. These anatomic relationships are demonstrated in the cadaver dissection of the anatomic snuffbox (Fig 2). That the dorsal radial artery is readily accessible was recently demonstrated by Mehigan and McAlexander (9) who performed arteriovenous fistulas for hemodialysis in this location with minimal dissection.

In addition to its superficial location, the size of the radial artery in the snuffbox is comparable to that at the wrist. Ten upper extremity arteriograms were reviewed and the radial artery diameters were measured at the volar and dorsal sites, mean diameter of the volar radial artery at the wrist was 2.3 mm. Mean diameter of the dorsal radial artery was 2.0 mm. As stated by Bedford (7), the relationship of the cannula diameter to arterial diameter is an important consideration. The incidence of arterial thrombosis increases as cannula diameter increases relative to vessel diameter, because blood flow around the cannula is reduced. As the arterial diameters are comparable at the two sites, blood flow around a 20-gauge cannula should be similar.

When a radial arterial catheter is inserted on the volar surface of the wrist, it is customary to immobilize the wrist in hyperextension. In contrast, when the dorsal insertion site is used, the hand is secured in the position of function. This position was readily tolerated by the patients in this series.

Cannulation of the dorsal radial artery as it emerges from the anatomic snuffbox is a safe alternative to cannulation of the artery on the volar aspect of the wrist. Successful cannulation was achieved in 35 of the 45 (78%) patients. This was our initial clinical experience with a new technique. It is anticipated that

FIG 1. Arteriogram of hand. Sites of volar and dorsal cannulation are marked by arrows. Site of dorsal cannulation is distal to origin of palmar branch of radial artery.

additional experience will result in an increased cannulation rate. Furthermore, percutaneous volar radial arterial cannulation is not always successful. Some patients require arterial cut-down for catheter insertion.

The principal advantage of this new technique is preservation of the palmar branch of the radial artery which is an important contributor to the superficial palmar arch. Sparing this important collateral vessel should decrease the incidence of digital ischemia. Additional experience is required.

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Somatosensory-Evoked Responses during Carotid Endarterectomy

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Carotid endarterectomy has become the definitive treatment for extracranial carotid artery disease associated with cerebrovascular insufficiency. The procedure includes clamping of the common, internal, and external carotid arteries during removal of the obstructive lesion and reconstruction. Every effort needs to be made to prevent ischemic brain damage during the reconstructive surgery. Because of individual variability in the effectiveness of collateral circulation through the circle of Willis, there are no reliable tests predicting ischemic brain damage during carotid artery clamping. To prevent a possible ischemic insult, some surgeons use a bypass shunt (1), whereas others refrain from using the shunt because of associated intimal damage, risk of embolization, and impediment to surgical procedure.

Because there is a risk of cerebral ischemia during carotid endarterectomy surgery, intraoperative monitoring using electroencephalograms (EEG) (2, 3), stump pressure (4), internal jugular venous P_{O_2} and oxygen saturation (5), and regional cerebral blood flow measurements with Xenon 133 has been suggested (6). Recently, evoked potentials have been found to provide a sensitive method of evaluating the function of different sensory components in the central nervous system (7). We have monitored cortical

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somatosensory-evoked responses (SERs) during carotid endarterectomy and found this to be a simple and useful method to detect cerebral ischemia promptly during surgery.

Methods

SERs were recorded in five patients who were undergoing carotid endarterectomy surgery using a cervical plexus block. Base line SERs were recorded the day before surgery and the sites of both stimulating and recording electrodes were marked on the skin with indelible crayon for subsequent placement during surgery. This preoperative assessment along with clinical evaluation allowed the SER monitoring equipment to be applied within a few minutes of the patient's arrival in the operating room.

All patients had radial arterial cannulation for measurement of arterial blood gas tensions and blood pressure. Electrocardiogram was continuously monitored. A complete neurologic examination including orientation in time and space, cranial nerves, motor system, sensory modalities, and superficial and deep reflexes was done before and after surgery. During surgery, the patient was repeatedly asked about day, time, place, counting numbers from 1 to 10 and from 10 to 1, movements of fingers and toes contralateral to the side of surgery, and any sensory symptoms such as tingling, numbness, or paresthesias.

The SERs were recorded by stimulating with square wave electrical impulses applied to the median nerves at both wrists by implanting needle electrodes over the median nerve to provide good contact and to minimize dislodgement. The scalp electrodes for recording were silver-silver chloride cup electrodes, attached to the skin with collodion and filled with electrode jelly.

Recordings were obtained from a parietal electrode placed 7 cm laterally and 2 cm behind the C_z electrode of the 10–20 International System, connected to a reference electrode placed at the F_z (midfrontal) position. In the preoperative assessment, records were obtained from both parietal areas following stimulation of each median nerve. During surgery, the SERs were evaluated visually from each side on the oscilloscope and were monitored primarily over the scalp ipsilateral to the endarterectomy in response to stimulation of the contralateral median nerve. If changes were observed over the ipsilateral scalp, the other median nerve was stimulated to compare the SERs on the two sides. The nerve was stimulated at a rate of

2/sec with 0.1- to 0.2-msec pulse duration and a constant current amplitude of less than 20 mamp. Stimulus strength was adjusted to a level that produced a visible but not maximal motor response of the abductor pollicis brevis. The frequency response of the system was 1 to 3 kHz (−3 dB). For analog-to-digital conversion, 256 data points were sampled during the analysis time of 250 msec following the stimulus. A total of 100 to 200 stimuli were averaged for each SER during surgery. The scalp responses were amplified 100,000 times, summed, and stored in an averaging computer (Nicolet Med-80). During surgery, the SERs were evaluated on the oscilloscope. The morphology, latencies, and amplitude of the SERs recorded during the period of carotid clamping were compared serially and also with the intraoperative preclamp study. Following the surgery, the results were graphed with a x-y plotter and transferred to a disc for permanent storage. Results were also analyzed after surgery by inspection of the graphed records. Analysis of the latencies and amplitudes was provided by direct cursor readout from the computer.

Normal SER following median nerve stimulation is best developed over the contralateral parietal areas and consists of a multiphasic potential. The individual peaks are designated as N_1, P_1, N_2, P_2, and N_3 in our laboratory, and the mean latencies of these peaks are 17.6, 23.2, 29.0, 37.9, and 62.9 msec, respectively.

Five patients between the ages of 68 and 78 years had carotid endarterectomy with analgesia provided by cervical plexus block. Intraoperative SERs were recorded at the beginning of surgery and after exposure of the carotid artery but before clamping for a base line evaluation. Following clamping, the SERs and neurologic assessment were monitored continuously. A shunt was introduced if neurologic symptoms were detected. SERs were also recorded during the reclamping of the carotid at the end of the endarterectomy for the removal of the shunt. Three patients had an unevenful carotid endarterectomy without any changes in SERs (as in patient 3 of the reported cases) and two patients had abnormalities of their SERs.

Case Reports

Case 1

A 67-year-old, 75-kg man with diffuse arteriosclerotic disease and right carotid artery stenosis producing transient ischemic attacks was operated upon for right carotid endarterectomy. Surgery was performed under cervical plexus block using bupivacaine, 225 mg, and 100 mg of chlorpro-

caine in 40 ml. Arterial systolic pressure was maintained between 160 and 180 mm Hg and Pa_{CO_2} between 27 and 29 mm Hg.

The SER recorded before surgery in the operating room was normal. The base line recording just before clamping of the right common carotid artery showed a well preserved SER (Fig 1, trace 1) as compared with the preoperative study. Immediately after clamping, the SER became lower in amplitude (Fig 1, trace 2), and after 7 minutes of clamping, the SER virtually disappeared (Fig 1, trace 3). With an increase in blood pressure after the intravenous administration of 0.2 mg of phenylephrine, SER returned to preclamping morphology even though clamping was continued since the patient's condition remained normal by continuous neurologic evaluation (Fig 1, trace 4). The right side SER remained unchanged during the procedure. The patient had no neurologic complications after surgery.

Case 2

A 76-year-old, 70-kg man with recurrent episodes of lower lateral quadrantic blindness in the right eye had a total occlusion of the right common carotid artery and 75% occlusion of the left common carotid artery at its bifurcation. A left carotid endarterectomy was performed under cervical plexus block using 450 mg of 1.5% mepivacaine in 30 ml. Arterial systolic pressure was maintained between 170 and 180 mm Hg and Pa_{CO_2} between 36 and 43 mm Hg with the patient breathing spontaneously with supplmented oxygen (3 L/min by nasal prongs).

SERs recorded in the operating room before the start of the surgery were similar to SER recorded in the laboratory on the day before surgery. The SER just before clamping of the left carotid was unchanged from the base line SER (Fig 2, trace 1). A continuous neurologic evaluation of the patient was done during the surgery by determining orientation to time and date, by asking the patient to move extremities to command, and to count forward and backward from 1 to 10. In addition, the patient was asked to report any symptoms of tingling or numbness.

Within 1 minute of clamping, when the stump pressures were being measured, the patient became dazed, nonresponsive, and showed twitching of the right angle of the mouth. SER showed loss of all waves except N_1, P_1 (Fig 2, trace 2). Immediately a bypass shunt was inserted. The patient became conscious and coherent within 1 minute and could perform all the tests by 3 minutes. The patient complained that he slept transiently. SER began to return to normal at 2 minutes and were normal at 4 minutes (Fig 2, trace 3) after placement of the shunt. Again during removal of the shunt for completion of the repair, carotid clamping resulted in the patient's becoming dazed and asphasic with loss of response to commands. The SER showed loss of morphology (Fig 2, trace 4), which returned within 4 minutes of the complete repair and removal of the clamp (Fig 2, trace 5). The SER recordings, clinical symptoms and signs, and blood pressure are shown in Fig 2. The

Trace Number	Procedure in Surgery	SER Trace	Latency Milliseconds	Amplitude Microvolts	Systolic Blood Pressure mm.Hg.	Clinical Features
1.	Just before carotid clamping		N_1 22.5 P_1 31.4 N_2 37.4 P_2 47.0 N_3 61.3	N_1 P_1 4.47 P_2 N_3 7.57	170	No clinical change
2.	2 minutes of clamping		N_1 23.5 P_1 31.5 N_2 37.2 P_2 50.0 N_3 Peak not identified	Decreased amplitude	160	No clinical change
3.	7 minutes of clamping		Altered morphology	Altered morphology	160	No clinical change. Phenylephrine 0.2 mg. I.V.
4.	9 minutes of clamping. 2 minutes after 0.2 mg. Phenylephrine		N_1 22.5 P_1 30.4 N_2 36.4 P_2 45.1 N_3 57.8	N_1 P_1 3.80 P_2 N_3 5.62	180	No clinical change
5.	10 minutes after repair		N_1 22.5 P_1 28.4 N_2 37.2 P_2 46.1 N_3 67.6	N_1 P_1 2.10 P_2 N_3 6.43	160	No clinical change

FIG 1. Somatosensory-evoked response (SER) in patient 1 showing changes following carotid artery clamping. Two minutes after clamping, morphology was completely changed and at 7 minutes there was loss of SER. By increasing blood pressure with phenylephrine, morphology of SERs returned to preclamp pattern. No neurologic symptoms were noted during these changes in SER. Total duration of clamping was 53 minutes. Stump pressure was 56 mm Hg.

patient's postoperative course was uneventful with normal neurologic status.

Case 3

A 74-year-old, 60-kg woman with a history of transient ischemic attacks and one episode of transient right upper limb weakness had 80% occlusion of the left common carotid artery at its bifurcation. A left carotid endarterectomy was performed with cervical plexus block using 200 mg of bupivacaine in 40 ml. Total duration of carotid clamping was 31 minutes. There were no changes in SERs or neurologic status (Fig 3). The postoperative course was uneventful.

Discussion

Complications associated with carotid endarterectomy surgery include myocardial infarction, cerebral infarction, acute internal carotid artery occlusion, postoperative stenosis requiring reoperation, seizures, and arterial or venous hemorrhage (8). The most serious complication is development of a stroke or progression of a preexisting neurologic deficit. The most common cause of neurologic deficit related to

the operative procedure itself is cerebral embolization with resultant cerebral ischemia. Clamping of the carotid artery during the procedure may also, however, result in neurologic deficits, particularly in patients with multiple large vessel disease, hypotension, or intracranial arterial thrombosis.

Routine use of a bypass shunt may obviate the need for intraoperative monitoring of cerebral function. Because of operative difficulties, embolization of atheroma, intimal damage, and interference with surgical technique, some surgeons use the bypass shunt only in selected patients. Hence it is imperative that proper monitoring be available and a bypass shunt be placed in patients showing evidence of inadequate collateral circulation.

Continuous EEG monitoring has been used during surgery. Technical difficulties with EEG monitoring include maintaining multiple electrodes and evaluation of enormous amounts of data, plus confusion in interpretation due to mild asymmetries. Some of these problems are solved by computer-assisted power spectral analysis of the EEG (9).

Determination of stump pressure is not a reliable

Trace Number	Procedure in Surgery	SER Trace	Latency Milliseconds	Amplitude Microvolts	Systolic Blood Pressure mm.Hg.	Clinical Features
1.	Just before carotid clamping		N_1 18.6 P_1 25.5 N_2 32.3 P_2 43.1 N_3 70.6	$N_1 P_1$ 5.51 $P_2 N_3$ 8.64	160	Cooperative. No neurologic symptoms.
2.	2 minutes of clamping		N_1 20.6 P_1 29.4 $N_2 P_2 N_3$ disappeared	$N_1 P_1$ 9.32 Altered Morphology $N_2 P_2 N_3$ disappeared	170	By one minute of clamping dazed, non-responsive. Twitching of right angle of mouth.
3.	4 minutes after shunt placement		N_1 19.6 P_1 23.5 N_2 31.4 P_2 46.1 N_3 67.6	$N_1 P_1$ 3.26 $N_2 P_2$ 9.67	174	Cooperative. Counts numbers. Moves fingers and toes. No sensory symptoms.
4.	2 minutes of clamping for shunt removal and repair		N_1 19.6 P_1 29.4 $N_2 P_2 N_3$ disappeared	$N_1 P_1$ 4.56 $P_2 N_3$ disappeared	176	Within 1 minute became dazed, aphasic, non-responsive.
5.	4 minutes after repair		N_1 17.6 P_1 24.5 N_2 32.3 P_2 44.1 N_3 73.5	$N_1 P_1$ 5.42 $P_2 N_3$ 7.85	166	Cooperative. No neurologic symptoms.

FIG 2. SER recordings in patient 2. Marked changes in SER and neurologic symptoms were noted with carotid clamping. A shunt was therefore inserted with return of SER to near pre-clamping configuration. N_2, P_2, and N_3 were complete y absent in SER when the carotid artery was clamped on two occasions, once at beginning of repair and once at time of removal of shunt. On both occasions, patient became unresponsive. Stump pressure was 23 mm Hg.

Trace Number	Procedure in Surgery	SER Trace	Latency Milliseconds	Amplitude Microvolts	Systolic Blood Pressure mm.Hg.	Clinical Features
1.	Just before clamping		N_1 22.5 P_1 30.4 N_2 37.2 P_2 56.8 N_3 101.9	$N_1 P_1$ 4.2 $P_2 N_3$ 18.5	200	No Change
2.	6 minutes of clamping		N_1 22.5 P_1 29.4 N_2 38.4 P_2 53.9 N_3 100.9	$N_1 P_1$ 5.2 $P_2 N_3$ 19.1	180	No Change
3.	30 minutes of clamping		N_1 20.6 P_1 29.4 N_2 38.2 P_2 51.9 N_3 98.0	$N_1 P_1$ 6.85 $P_2 N_3$ 17.3	200	No Change
4.	10 minutes after repair		N_1 22.5 P_1 29.4 N_2 37.4 P_2 53.9 N_3 98.0	$N_1 P_1$ 8.31 $P_2 N_3$ 18.1	200	No Change

FIG 3. SER recordings in patient 3 who had left carotid endarterectomy. SER showed no changes during carotid artery clamping for 30 minutes.

CLINICAL REPORTS

method for assuring adequacy of cerebral blood flow during carotid clamping.

We believe that SER monitoring following median nerve stimulation during carotid endarterectomy provides a relatively simple but reliable method of evaluating cerebral function and adequacy of collateral circulation. The technique of monitoring SERs requires placing only five electrodes. The SERs generated every minute (100 responses) can easily be compared serially and bilaterally to detect a significant change. Reduction in amplitude, prolongation of latencies, or distortion of the wave form of the SER suggests the probability of cerebral ischemia requiring the use of a shunt. On the other hand, continued preservation of the SER following carotid clamping indicates adequacy of collateral circulation (patient 3, Fig 3). Comparing the SERs on the operative side with those on the nonoperative side when changes are noted should exclude systemic causes, such as anesthesia or hypotension, and equipment malfunction.

Carotid endarterectomy in patients in this report was not followed by neurologic complications because of early intervention with a shunt (patient 2) or because cerebral perfusion was improved by increasing the blood pressure (patient 1) when SER changes were noted. Patient 1 demonstrated no clinical neurologic deficit during surgery although SERs demonstrated changes in morphology following clamping of carotid vessels (Fig 1). However, continued monitoring and increasing the systolic blood pressure from 160 to 180 mm Hg resulted in return of the morphology of the SERs to preclamping pattern; this was probably due to improved collateral blood flow. The above observation suggests that a change in SER morphology may be an early warning of decreased perfusion even before occurrence of a clinically evident neurologic deficit. Symon et al (10) recorded the central conduction time in patients with subarachnoid hemorrhage. The central conduction time evaluates function of the somatosensory pathway within the brain by recording evoked potentials from the neck and scalp. Prolongation of latency (10) or reduction in amplitude (11) of SERs have been found to indicate

ischemic changes in the brain. An increase in the conduction time has been suggested to be a sensitive monitor for hemispheric dysfunction before the onset of a clinical deficit.

We conclude that continuous SER monitoring during carotid endarterectomy is a useful technique to detect early central nervous system dysfunction from hypoperfusion and possibly indicates the need to institute a bypass shunt. SERs are also easier to interpret under clinical conditions than is the EEG.

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letters
TO THE EDITOR

New Adaptor for Intravascular Electrocardiogram

To the Editor:

In 1970, Martin (1) reported a method for accurate positioning of a central venous catheter tip, using the intravascular electrocardiogram (ECG) derived from the catheter itself. He connected a sterile metal insert to the central venous catheter and linked the insert to the ECG chest lead by an alligator clip to record the intravascular ECG. W-shaped P waves on the ECG indicated when the tip was at the superior cavoatrial junction.

This method, although convenient and easily learned, is slightly troublesome because measuring line necessitated collecting a sterile metal three-way stopcock and a connecting alligator clip.

We have devised a new connecting tube adaptor with alligator clip that is sterile, disposable, and always ready for use. As shown in the Figure, the

fine thread wire is in the vinyl tube adaptor and is connected to the shielded alligator clip. The intravascular ECG can easily be recorded by filling the adaptor and central venous catheter with heparinized saline and connecting the alligator clip to the ECG chest lead. Right atrial catheterization, monitored by the intravascular ECG using the new adaptor, was performed in 70 patients undergoing neurosurgery in the sitting position. All catheter tips were accurately placed at the superior cavoatrial junction without complications. Correct placement was confirmed by roentgenogram. This new adaptor is useful when the intravascular ECG is used as a guide to correct positioning of central venous catheters.

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heparinized saline

fine thread wire

CVP catheter

alligator clip

chest lead of ECG monitor

FIGURE. New adapator for intravascular electrocardiogram.

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Plasma Catecholamine Levels

To the Editor:

Brown et al (1) measured the perioperative hormonal and cardiovascular responses of patients undergoing abdominal surgery anesthetized either with fentanyl (4.5 $\mu g/kg$)/66% N_2O or with 1% to 4% inspired enflurane/50% N_2O. I believe their conclusion that "enflurance anesthesia blocks the sympathetic response to surgical stress more effectively than low-dose fentanyl anesthesia" is poorly substantiated. In the Figure, I have plotted their data for plasma venous levels of epinephrine and norepinephrine. It is true that the intraoperative norepinephrine level (surgery, Figure) is significantly greater (statistically) in the patients receiving fentanyl anesthesia compared with those receiving enflurane anesthesia (asterisk). However, is it not more important to conclude that with either anesthetic technique, the norepinephrine and epinephrine levels increase significantly from control levels (Figure, plus sign) in both the intraoperative and postoperative periods?

If there is a reduced sympathetic response to surgical stress during enflurane anesthesia compared with fentanyl anesthesia, as Brown et al. (1) propose, then we should also see a reduced cardiovascular response to

+ p< 0.05, compared to control
* p< 0.05, between groups

FIGURE. Venous plasma levels of epinephrine and norepinephrine during four perioperative periods in patients anesthetized with fentanyl/N_2O or enflurane/N_2O. Intraoperative determinations of norepinephrine were significantly greater in patients anesthetized with fentanyl compared with those anesthetized with enflurane. However, more importantly, patients anesthetized with either technique had significantly greater levels of both catecholamines during intraoperative and recovery room periods, compared with control values. In general, highest levels of catecholamines were found during recovery period. Data derived from Brown et al (1).

TABLE

Comparison of Fentanyl (F) and Enflurane (E)*

	Control		After induction		Surgery			Recovery	
	F	E	F	E	F		E	F	E
SBP (torr)	134	139	126	120	143	†	121	147	147
HR (beats/min)	79	88	80	86	87	†	98	78	89
RPP	10,586	12,332	10,080	10,320	12,441		11,858	11,466	13,083

* Abbreviations used are: SBP, systolic blood pressure; HR, heart rate; RPP, rate-pressure product.
† p < 0.05 between groups.

surgical stress in the patients receiving enflurane anesthesia. However, from their systolic blood pressure and heart rate data, which are shown in the Table, the authors state (1), "one cannot conclude [that either the fentanyl technique or the enflurane anesthesia technique] is more beneficial than the other with regard to the myocardial workload or myocardial oxygen consumption. I would go even farther and suggest that when examining the rate-pressure products calculated from their data (see Table), although there is no statistically significant difference between the two patient groups, it appears that patients receiving fentanyl/N_2O anesthesia have a more favorable blood pres-

sure/heart rate relationship. Compared with enflurane-anesthetized patients, patients given fentanyl have a higher blood pressure and lower heart rate, permitting greater coronary blood flow and myocardial perfusion. Nevertheless, I believe the best substantiated conclusion from all these data is that neither enflurane anesthesia nor "low-dose" fentanyl anesthesia is able to adequately prevent hormonal and cardiovascular "stress" responses during surgery.

Perhaps even more important is our understanding that, in general, the greatest stress, as indicated by elevations of levels of epinephrine or norepinephrine, or rate-pressure product, occurs during the recovery

period (Figure and Table). Interestingly, the highest measured epinephrine levels occurred in patients recovering from enflurane/N_2O anesthesia. This may be expected in view of the fact that other stress-producing phenomena, such as shivering, are more likely seen in patients recovering from inhalational anesthesia compared with those recovering from N_2O/narcotic anesthesia (2). If preventing a stress response is felt to be important, then we should attempt to prevent the stress response during the recovery period as aggressively as we attempt to prevent the response to intubation and surgical incision.

It is not surprising that N_2O/O_2 anesthesia supplemented with either enflurane (1% to 4%, inspired) or fentanyl (4.6 μg/kg) permits patients to demonstrate perioperative hormonal and cardiovascular responses to the stress of a 2-hour surgical procedure. Although Brown et al (1) have shown that with either technique, the sympathetic response to intubation may be prevented, they have found, as have others, that anesthesia with inhalation anesthetics or with low to moderate doses of fentanyl does not reliably prevent intraoperative or postoperative responses to surgical stress (3, 4). In any given patient, if abolition of the "stress response" to intubation, incision, and surgery is viewed as mandatory, then much higher doses of fentanyl must be used with the understanding that postoperative ventilation may be required.

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To the Editor:

Apparently, Dr. McLeskey does not disagree with the experimental methods as he only takes exception to the interpretation of the data. Data are presented in their original form so that each reader can make his/her own interpretation. However, the statement in the original abstract remains valid: ". . . enflurane anesthesia blocks the sympathetic response to surgical stress more effectively than low dose fentanyl anesthesia" (1).

We did not address the problem of stress response during recovery from anesthesia and surgery. However, our data do show an increased stress response following anesthesia and surgery. As McLeskey has stated, during recovery, plasma levels of epinephrine were lower following low dose fentanyl than following enflurane anesthesia. Although shown in the original data, he does not point out that there is also a substantially higher level of serum norepinephrine following low dose fentanyl than enflurane during the recovery phase. In addition, total serum catecholamine levels were higher in the fentanyl group.

McLeskey speaks of a more favorable blood pressure/heart rate relationship with fentanyl/N2O anesthesia. Certainly, rate-pressure product is widely used, but we know of no data concerning the interrelationship of the two at the levels measured. Exploring this area might be rewarding, but it is not useful in comparing the two techniques at this time (without documentation). Indeed, McLeskey's recapitulation of rate-pressure product shows a modest advantage of enflurane during surgery.

We do not disagree with McLeskey's call for aggressive treatment of the stress response during recovery. In fact, this should be true regardless of the operative anesthetic used. Most of our patients, regardless of technique, receive analgesics in the recovery phase, but we did not use analgesics during this study to avoid confusing the methods or resultant data.

McLeskey apparently inferred that the postinduction phase was used for measuring responses to intubation. Although not explicitly stated in the article, the reason for obtaining samples during this phase was to determine whether the groups remained

similar before the stimulation of surgery occurred. The timing of these samples was not related to intubation. Samples were taken just before skin incision, by which time the transient stimulation of intubation had passed.

Paraphrasing our statement in the original article, in constructing our study we wished to compare two techniques from which one could reasonably expect the patient to awaken and be extubated in the operating room. Therefore, we used low dose techniques for our fentanyl patients. Higher dose ranges have been shown to be associated with lower plasma catecholamine levels during surgery (2), but, frequently, require postoperative ventilation. Our study is clear in showing that fentanyl has no such advantages in dose ranges that are likely to allow rapid recovery.

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Dual-System Hypothesis of Pain Perception: Possible Further Evidence

To the Editor:

The finding of Abram et al (1), that naloxone at two different low concentrations did not influence transcutaneous electrical stimulation may be open to a different interpretation. This is particularly so if the data presented are carefully considered, as there seems to be a tendency for the

lower dose of naloxone to have caused a reduction in pain intensity, although the higher dose of naloxone shows a tendency to reverse analgesia. This tendency did not reach statistical significance in the study of Abram et al.

It is our contention, nevertheless, that had they used even lower concentrations of naloxone (less than 0.4 mg) potentiation of analgesia may well have occurred, whereas higher doses (greater than 2 mg) may well have caused significant reversal of analgesia. This suggestion is based on our work, in which we have shown that naloxone at concentrations less than 2 mg resulted in a biphasic response (2) when given during nitrous oxide-induced analgesia associated with a painful mechanical stimulus. In most cases the nitrous oxide analgesia was potentiated by concentrations of naloxone less than 2 mg, but in some cases reversal of analgesia did occur. Furthermore, in this work we found the maximum response to manifest itself within 3 minutes of intravenous bolus administration of naloxone.

This biphasic response of naloxone has been shown on a number of occasions (3–6). To explain this paradoxical effect of naloxone, we have suggested that a dual system may exist in which low doses of naloxone would tend to alter the equilibrium of an opiate and anti-opiate system in favor of analgesia, whereas at higher concentrations of naloxone the equilibrium would be shifted toward hyperalgesia (7).

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Vasodilation with Nitroprusside and Nitroglycerin

To the Editor:

I wish to comment on the recent article by Gerson and colleagues (1), in which the authors attempted to quantitate vasodilator-induced changes in venous capacitance by measuring changes in the volume of blood contained in the oxygenator reservoir during cardiopulmonary bypass. Although reservoir volume is undoubtedly influenced by venous capacitance, a number of confounding variables render invalid the assumption that reservoir volume changes indicate equal and opposite changes in venous capacity. I have borrowed and only slightly modified concepts and equations from Guyton et al (2) to illustrate my argument.

A simplified schema of the circulation that considers the pump-oxygenator to be one segment and the systemic arterial and venous vascular trees to be two other major segments of the circulation is presented in the Figure. Resistance Ra is the resistance from the midpoint of the arterial vascular tree to the midpoint of the venous tree. Resistance Rv is the resistance from the midpoint of the venous tree to the pump-oxygenator. Capacitance Ca is the capacitance of the arterial tree and capacitance Cv is the capacitance of the venous tree. Pressure Pa is the systemic arterial pressure and Pv is the pressure at the midpoint of the venous tree. Volume EVa is the extra volume in the arterial tree over and above the amount required to fill the arterial tree without
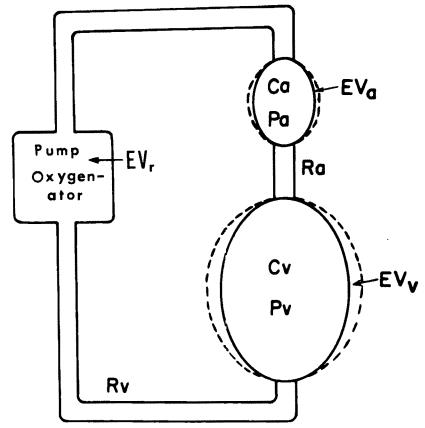
FIGURE. Schematic model of circulation during cardiopulmonary bypass (after Guyton et al[2]).

any pressure. Volume EVv is the extra volume in the venous tree in addition to the amount that barely fills the vessels without any pressure.

The pressures in the arteries and veins are equal, respectively, to the pressure drop from the arteries to the pump-oxygenator or from the veins to the pump-oxygenator. The pressure in the pump-oxygenator is assumed to be zero. Thus, if pump-output equals cardiac output (CO) then

$$Pv = CO (Rv) \qquad (1)$$

$$Pa = CO (Rv + Ra) \qquad (2)$$

The extra volume in each of the two major vascular trees is equal to the pressure times the capacitance, the capacitance being defined as dV/dP. Thus, utilizing the pressures from equations 1 and 2, we derive the following:

$$EVv = CO (Rv) (Cv) \qquad (3)$$

$$EVa = CO (Rv + Ra) (Ca) \qquad (4)$$

The total extra volume in the cir-

cuit EVt is equal to the extra volume in the venous and arterial trees, plus the extra volume in the oxygenator reservoir EVr. Thus,

$$EVt = EVa + EVv + EVr \qquad (5)$$

Substituting equations 3 and 4 into equation 5 and solving for EVr, we obtain the following

$$EVr = EVt - CO [Rv (Cv) + (Rv + Ra) Ca] \qquad (6)$$

According to equation 6, if no volume is added to or lost from the system and pump-output is held constant, then an isolated increase in venous capacitance will certainly decrease reservoir volume, as suggested by Gerson et al (1). Unfortunately, vasoactive compounds such as nitroglycerin and nitroprusside may also influence the three other factors in the equation simultaneously (i.e., Ra, Rv, and Ca). Furthermore, the effects of these agents on resistance and capacitance will tend to have opposing effects on reservoir volume which may cancel one another. For example,

the tendency of nitroprusside to decrease vascular resistance will tend to increase reservoir volume, whereas its capacitance effects will tend to counteract this. Of special importance might be the difference in the effects of such drugs as nitroglycerin and nitroprusside on venous resistance. Because of the relatively large value of Cv, small changes in Rv might have a great influence on reservoir volume. The measurements of systemic vascular resistance of Gerson et al (1) do not discriminate between changes in venous and arterial resistance.

To complicate matters further, conventional cardiopulmonary bypass techniques may produce subambient central venous pressures, resulting in the collapse of exposed portions of the venous capacitance below unstressed volume. Under these circumstances, the venous reservoir could conceivably undergo some volume changes independent of Pv or Cv.

In view of equation 6, I feel that the conclusions of Gerson et al (1) are tenuous. Nitroprusside may exert potent effects on venous capacitance that are not reflected in changes in oxygenator reservoir volume because its effects on resistance vessels have an opposing influence on venous return. This argument is supported by the failure of the authors to demonstrate differing effects of the two agents on forearm venous tone at any dose.

In conclusion, I would reemphasize that the above analysis, insofar as it proves useful, was derived completely from vital concepts of circulatory physiology propounded by Guyton et al (2). Any weaknesses or errors in the argument are my own responsibility.

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To the Editor:

We thank Dr. Thomson for his interest, and for raising some valid questions about our article (1). His adaptation of Guyton's theoretical model appears basically correct, but has limited practical application. To avoid confusion, we will use the definitions and abbreviations that Thomson has provided; we will also use SNP for nitroprusside and NTG for nitroglycerin.

Thomson's concerns may be summarized as follows: (a) Collapse of surgically exposed portions of the great veins may alter venous reservoir volume. (b) Measurements of systemic vascular resistance (SVR) do not discriminate between changes in venous and arterial resistance. (c) Venous reservoir volume (EV_r) may be affected by changes in arterial volume (EV_a) as well as by changes in venous volume (EV_v). (d) "Furthermore, the effects of these agents [SNP and NTG] on resistance and capacitance will tend to have opposing effects on reservoir volume which may cancel one another."

Our responses to these points are:

a. Collapse of the great veins exposed to atmospheric pressure would create a Starling resistor, limiting the narrowed region to a short segment. Collapse of a small portion of the vena cava would result in only a minimal volume change, and should, in any case, remain constant during both control and experimental time periods. Supporting this, mean subclavian central venous pressure in our patients was 1.0 ± 1.7 (SD) mm Hg and did not change with SNP or NTG infusion.

b. $SVR = (Pa - CVP)/pump$ output. The standard formula for SVR does not separate R_a from R_v. It does include R_a and R_v, however. The usual ratio of $R_a{:}R_v$ is 7:1 (2). Thus, changes in SVR are mainly due to changes in arterial resistance. The major reason for using SVR, however, is that R_a and R_v cannot be readily measured clinically (how does one find the "midpoints" of the arterial and venous trees?).

c. Volume leaving the venous reservoir could conceivably go to the arterial as well as the venous tree as Thomson states. But, the veins are the primary volume reservoir of the circulation (2, 3). Their capacitance is

some 18 times that of arteries (2). Roughly 70% of the body's blood volume resides in the veins (4), and acute blood volume changes are buffered mainly by the veins (3). Thus, changes in EV_r should best reflect changes in EV_v. Our conclusion that NTG dilates veins primarily is further supported by our finding of no change in SVR (primarily an arterial variable) with NTG.

d. This is largely a semantic problem. We used the term "venous capacitance" once in "Methods," whereas in our conclusions and elsewhere the term "venous dilation" was used. We did not intend to use Guyton's definition of "venous capacitance" nor was "venous dilation" meant to be synonymous with that definition. Our intent was to represent those decreases in venous reservoir volume that were due to patient uptake of volume. We believe, for the reasons cited above, that most of this volume was taken up on the venous side. We regret any confusion that our terms may have caused.

As C_a and C_v and R_a and R_v cannot be measured directly in our model, Thomson's argument is theoretically possible. But its utility in helping the clinician decide whether to use NTG or SNP is limited. Looking at Thomson's equation (5), as EV_t is assumed constant, the observed decrease in EV_r must have been matched by an increase in EV_v and/or EV_a. The drug that most decreased EV_r, NTG, is thus better for use in sequestering volume. We cannot be sure whether the effect of SNP on resistance or capacitance (after Guyton et al (2)) makes it less suitable than NTG to sequester volume. But our conclusion (1), "At equal doses NTG would be expected to better decrease venous return to the heart and thus reduce preload or compensate for overtransfusion, whereas SNP would be expected to better decrease arterial pressure ..." is in no way affected by Thomson's analysis.

Further justification for the experimental model we used is provided by Hsu et al (5).

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book

REVIEWS

Anesthetic Considerations in the Surgical Repair of Intracranial Aneurysms, edited by G. P. Varkey, Boston, Little, Brown and Co., 1982, 243 pp, $40.00/quarterly.

This book is largely a description of methods used at The University of Western Ontario Faculty of Medicine for anesthetic management of patients with intracranial aneurysms. Of the 20 chapters in the main part of the book, 13 were written by members of the Western Ontario group. Only one chapter in this section was written by an author in the United States. The second section of the book briefly describes methods used in six other centers, two of them in the United States.

The Western Ontario group has had vast experience with operative treatment of intracranial aneurysms. A more detailed description of their series of cases seems warranted. Nevertheless, many of the methods used in Western Ontario have not gained general acceptance in other institutions. Although the second section of the book gives recognition to the fact that different methods can be used, the book achieves no synthesis describing and analyzing the controversies in the field. Thus, the volume is essentially a "how I do it" manual rather than a scientific treatise.

The outstanding chapters in the main section of the book are those on the surgical repair of intracranial aneurysms and on the effects of anesthetics on cerebral blood flow and intracranial pressure. Fewer chapters might have reduced repetition and

allowed more complete discussion of important and controversial topics. Coverage of many areas is spotty and arbitrary, with little analysis of rationale for alternative approaches and too little presentation of data.

The chapter on preanesthetic evaluation should be in the section on preoperative considerations. The two chapters by Ferguson might have been combined, and the justification for separate chapters on spontaneous ventilation and on the Bain circuit is not apparent.

Several authors mention classification of patients whose aneurysms have bled, but nowhere are the classifications described. In contrast, much material is so rudimentary as to be superfluous. Imprecise and colloquial terminology appears, as when "the anesthetist prefers to 'stone' the patient." Trade names are used more often than necessary.

Several unsupported overstatements are found. Few would agree, for example, that pathologic coma is a "protective response" to brain injury or that this concept was the basis for attempts to protect the brain pharmacologically. The chapter on electroencephalographic (EEG) monitoring is a useful addition, but the absence of EEG changes in a single-channel contralateral to the craniotomy should not necessarily encourage the authors to proceed at extreme levels of hypotension.

Despite its limitations, this book will be useful to anesthesiologists interested in an empirical description of anesthetic techniques used to manage patients with intracranial aneurysms in Western Ontario and a few other centers, mostly in other countries. Readers who expect a synthesis of current knowledge in the field with an analytic description of controversial areas will be disappointed.

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Physical Evaluation of the Dental Patient, by C. L. Halstead, G. G. Blozis, A. J. Drinnan, and R. E. Gier, St. Louis, C. V. Mosby Co., 1982, 422 pp, $29.50.

The addition of this text to the dental literature could not have come at a more opportune time. Changes in the philosophy of dental care are taking place rapidly. Dentists realize they no longer have the luxury of treating only healthy patients. It is this concept that promoted the authors to assemble this comprehensive text. The writing may be a bit ahead of its time as far as wide acceptance into the dental curriculum at an undergraduate level is concerned, but the fact that the Joint Commission on Accreditation of Hospitals now permits qualified oral and maxillofacial surgeons to perform admitting history and physical examinations for hospitalized patients attests to the appropriateness of this text in the profession of dentistry as a whole.

Throughout the text the reader is reminded of the importance of identifying pathologic states that may have been otherwise undetected. Emphasis is placed on the significance of understanding the pathophysiology of conditions with which patients are seen. The necessity to consult and communicate intelligently with treat-

ing physicians when required is also stressed.

Chapters dealing with basic principles and techniques of physical evaluation, diagnostic process, the health record, and patient interviewing are clearly and concisely written. Those chapters detailing the specifics relative to the review of each system are well illustrated and progress in a logical and organized manner. To the astute diagnostician these chapters may appear a bit superficial. However, the intention of the authors was to write a basic text that "offers a reasonable and attainable level of understanding about an important area of dental practice." The objective reaches its goal.

Perhaps the title is a little misleading as nearly half of the book is devoted to identification of dental con-

ditions that for the most part are dealt with in greater detail in other books. Nonetheless, this one-of-a-kind text is certain to make a valuable contribution to the changing field of dental patient care.

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Pittsburgh, PA

BOOKS RECEIVED

Some Aspects of Paediatric Anesthesia, edited by D. J. Steward, The Netherlands,

Elsevier Biomedical Press BV, 1982, 377 pp, $95.00.

Drugs and Anesthesia (Pharmacology for Anesthesiologists), edited by M. Wood and A. J. Wood, Baltimore, Williams & Wilkins, 1982, 746 pp, $57.00.

A Lawyer Looks at Abortion, by L. D. Wardle and M. A. Wood, Salt Lake City, Brigham Young University Press, 1982, 280 pp, $7.95.

The Clinical Core of Respiratory Medicine, by C. R. Woolf, Philadelphia, JB Lippincott, 1981, 304 pp, $18.50.

Toxicity of the Metabolites of Inhalation Anesthetics, by P. H. Rosenberg, New York, Gustav Fischer Verlag Publishers, 1982, 62 pp, DM 34.00 (price for subscribers to the whole series).

A Guide for Authors

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Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

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2. Corporate Author

    The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119–25.

    Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224–5.

Books and Other Monographs

3. Personal Author(s)

    Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

    American Medical Association Department of Drugs AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

    Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

    Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

7. Agency Publication

    National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968–June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72–1036).

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*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., et al.: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

References:
1. Bunker, J.P., et al.: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology 43:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

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FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), up to 0.00025% ammonia (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation.

FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is

possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

It has been reported that in genetically susceptible individuals, the use of general anesthetics and the muscle relaxant, succinylcholine, may trigger a syndrome known as malignant hyperthermic crisis. Monitoring temperature during surgery will aid in early recognition of this syndrome. Dantrolene sodium and supportive measures are generally indicated in the management of malignant hyperthermia.

Adverse Reactions. The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

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Surgical procedures are perceived as frightening or unpleasant by most patients. If given the opportunity, many would rather not remember anything about the ordeal.

Ativan® Injection can help. Administered as recommended, Ativan Injection helps sedate the patient, relieves presurgical anxiety and diminishes recall of events surrounding surgery.

The dosage of Ativan Injection should be individualized for each patient. For those patients in whom a lack of recall and excellent sedation are desired, doses of 0.05 mg/kg up to a maximum of 4 mg should be administered. For patients in whom a lack of recall is not desired, as well as for the elderly or debilitated, the dose of Ativan Injection should be reduced.

See important information on following page.

Wyeth Laboratories
Philadelphia, PA 19101

ATIVAN® (LORAZEPAM) ℂⅣ
INJECTION IM or IV

ATIVAN® (LORAZEPAM) Ⓒ
INJECTION IM or IV

DESCRIPTION: Ativan* (lorazepam) injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzo-diazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal *failure*. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately post-injection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure.* Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure.* EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan* (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX* Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581, 10 ml vial and 1 ml fill in 2 ml TUBEX.

4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.

For IM or IV injection.

Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

Wyeth Laboratories
Philadelphia, PA 19101

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THE ANXIETY OF INDUCTION

CALM THE APPREHENSION WITHIN MINUTES WITH INJECTABLE VALIUM (diazepam/Roche) I.V.

You've seen the signs of anxiety hundreds of times. Palpitations. Tremulousness. Diaphoresis. Hyperventilation. Ordinary patients about to undergo an extraordinary ordeal: the physical and emotional traumas of neuromuscular blockade, anesthesia and surgery.

When you administer an antianxiety agent to these patients just before the procedure, you want a prompt, predictable anxiolytic response. And that is exactly what you achieve with Injectable Valium (diazepam/Roche) I.V.

Usually within three minutes, patients grow noticeably calmer after an intravenous injection of Valium.[1,2]

In most instances the patient falls into a light sleep, yet can still be easily aroused to respond to your instructions. This allows you to proceed directly with intubation, neuromuscular blockade and/or anesthesia. Other anxiolytics lack the rapid action of Injectable Valium I.V., and may take up to 20 minutes or more to produce adequate sedation—a long time to wait before beginning the procedure. The rapid sedative action of Injectable Valium I.V. gives you the control you need in the critical minutes before intubation. Dosages of concomitantly administered narcotic analgesics should be reduced by at least one-third and administered in small increments. In some cases, the use of a narcotic may not be necessary.

Ready to use—needs no reconstitution or refrigeration In further contrast to other injectable anxiolytics, which may require dilution before being used, Injectable Valium I.V. needs no reconstitution. Do not mix or dilute Valium with other drugs or solutions in syringe or infusion flask; administer slowly directly into a large vein, or inject slowly through the infusion tubing as close as possible to the vein insertion site. Take at least one minute for each 5 mg (1 ml).

During storage, there is no need to refrigerate Injectable Valium—another advantage over other injectable agents.

DIMINISH RECALL OF THE PROCEDURE WITH INJECTABLE VALIUM (diazepam/Roche) I.V.

Recall of endotracheal intubation or other psychologically disturbing events associated with anesthetic induction and surgery can be largely prevented with Injectable Valium I.V.

A survey of the literature shows that 2586 of 2707 patients (95%) had partial or total lack of recall when Injectable Valium (diazepam/Roche) I.V. was given as premedication for procedures in cardiac and plastic surgery, fracture reductions, gynecologic surgery, oral surgery and ophthalmic surgery.[3] The anterograde amnesia produced after an intravenous injection of Valium usually begins to take effect within three minutes, peaks within 10 minutes and persists for 20 to 60 minutes.[2,4-7]

Minimal effect on cardiac and respiratory function
A review of published reports involving more than 12,000 patients administered Injectable Valium—including patients with coronary artery disease—shows that clinically significant blood pressure changes, alterations in basal circulatory parameters or increased incidence of hypotension, tachycardia or bradycardia are rare when recommended procedures for dosage and administration are followed. Clinically significant respiratory depression is also rare with Injectable Valium I.V. in subjects without respiratory disease (0.3% incidence in more than 12,000 patients).[3]

Facilities for respiratory assistance, however, should be readily available. When administering Injectable Valium I.V. to the elderly, to very ill patients or to patients with limited pulmonary reserve, lower doses (usually 2 mg to 5 mg) and slow increase in dosage should be used because of the possibility that apnea and/or cardiac arrest may occur. Concomitant use of barbiturates or other CNS depressants increases depression with increased risk of apnea. As with most CNS-acting drugs, patients should be cautioned against drinking alcohol or operating hazardous machinery.

So when anxiety mounts in the face of induction, choose the I.V. agent with a rapid, predictable anxiolyic effect...

RAPIDLY AND PREDICTABLY CALMED WITH

INJECTABLE VALIUM® I.V.
(diazepam/Roche) Ⓘ

Ready-to-use, 2-ml Tel-E-Ject® disposable syringes
2-ml ampuls, 10-ml vials — 5 mg/ml

See next page for references and summary of product information.

⟨ROCHE⟩

References: 1. Diazepam and lorazepam in anaesthesia. *Drug Ther Bull* 17:19-20, Mar 2, 1979. **2.** Conner JT et al: *J Clin Pharmacol* 18:285-292, May-Jun 1978. **3.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **4.** George KA,

Dundee JW: *Br J Clin Pharmacol* 4:45-50, Feb 1977. **5.** Dundee JW, Pandit SK: *Br J Pharmacol* 44:140-144, Jan 1972. **6.** Gregg JM, Ryan DE, Levin KH: *J Oral Surg* 32:651-664, Sep 1974. **7.** Clarke PRF et al: *Br J Anaesth* 42:690-697, Aug 1970.

INJECTABLE VALIUM® (diazepam/Roche) Ⓘ

Please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated w th the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given, do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; re-administer if necessary; not recommended for long-term maintenance therapy. If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), i.e., phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function, avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice, periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcohol withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, administer I.V. slowly; for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred), repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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Dundee JW. *Br J Clin Pharmacol 4* 45-50, Feb 1977. **5.** Dundee JW, Pandit SK. *Br J Pharmacol 44* 140-144, Jan 1972. **6.** Gregg JM, Ryan DE, Levin KH. *J Oral Surg 32* 651-664, Sep 1974. **7.** Clarke PRF et al. *Br J Anaesth 42* 690-697, Aug 1970.

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Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest, concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea, have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence, can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return, re-administer if necessary; not recommended for long-term maintenance therapy. If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), i.e., phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcohol withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses), in children, administer I.V. slowly, for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred), repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M., in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

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The soft, flexible tube, smooth bevelled tip and high volume, low pressure cuff work together to reduce possible mucosal trauma during intubation and in use. Reference depth marks 2 and 4 cm above the cuff facilitate proper tip replacement. Tight sealing of the reinforcing wire against the connector lowers the potential for kinking even at this "high-risk" junction.

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- Reinforcing wire is permanently sealed against the connector for added resistance to kinking.
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*Ng TY, Kirimli BI: Hazards in Use of Anode Tracheal Tube: a Case Report and Review. Anesthesia and Analgesia, 54:710. 1975.

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(enflurane)

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control of depth

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ETHRANE® (enflurane)

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CAUTION: Federal Law Prohibits Dispensing without a Prescription.

DESCRIPTION

ETHRANE (enflurane) (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether) (CHF2OCF2CHFCl) is a nonflammable inhalation anesthetic agent. The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation.

$$\log_{10} P = A + B/T \quad A = 7.967$$
$$B = -1678.4$$
$$T = °C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20°C is 1.3025-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C.

Enflurane is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary even in the presence of ultraviolet light. Enflurane is stable to strong base and does not decompose in contact with soda lime and does not react with aluminum, tin, brass, iron or copper. The partition coefficients of enflurane at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ETHRANE (enflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70 percent nitrous oxide—30 percent oxygen, and 1.17 in 30 percent nitrous oxide—70 percent oxygen.

[The remainder of the Clinical Pharmacology section, including sections on induction and recovery, blood pressure, cardiac rhythm, muscle relaxants, biotransformation, and obstetrics, is printed in small type and is largely illegible.]

INDICATIONS AND USAGE

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Enflurane may be used to provide analgesia for vaginal delivery. Low concentrations of enflurane (see DOSAGE AND ADMINISTRATION) may also be used to supplement other general anesthetic agents during delivery by Cesarean section. Higher concentrations of enflurane may produce uterine relaxation and an increase in uterine bleeding.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).
Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.
Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentrations usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged enflurane anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to depth of anesthesia. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

PRECAUTIONS

The action of nondepolarizing relaxants is augmented by ETHRANE (enflurane). Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from neuromuscular blockade will be longer in the presence of enflurane than when halothane or nitrous oxide with a balanced technique are used.

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. Enflurane should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug.

In susceptible individuals, enflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc. The syndrome of malignant hyperthermia secondary to enflurane appears to be rare; by March 1980, 35 cases had been reported in North America for an approximate incidence of 1/725,000 enflurane anesthetics.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO2 absorption system (hot canister). PaCO2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., enflurane), administration of intravenous dantrolene, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. Renal failure may appear later, and urine flow should be sustained if possible.

Swiss ICR mice were given enflurane to determine whether such exposure might induce neoplasia. Enflurane was given at ¼, ½, and ⅛₂ MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice who were given the same background gases, but not the anesthetic.

Exposure of mice to 20 hours of 1.2 percent enflurane causes a small (about ¼ of 1%) but statistically significant increase in sperm abnormalities. In contrast to these results, in vitro approaches to the study of mutagenesis (Ames test, sister chromatid exchange test, and the 8-azaguanidine system) have not shown a mutagenic effect of enflurane.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to enflurane. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

ADVERSE REACTIONS

1. Malignant hyperthermia.
2. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
3. Hypotension and respiratory depression have been reported.
4. Arrhythmias, shivering, nausea, and vomiting have been reported.
5. Elevation of the white blood count has been observed.

OVERDOSAGE

In the event of overdosage, the following action should be taken:
Stop drug administration; establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using
a) vaporizers calibrated specifically for enflurane;
b) vaporizers from which delivered flows can easily and readily be calculated.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by enflurane and that enflurane does not alter heart rate. The use of anticholinergic drugs is a matter of choice.

Surgical Anesthesia: Induction may be achieved using enflurane alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the enflurane mixture. In general, inspired concentrations of 2.0-4.5 percent enflurane produce surgical anesthesia in 7-10 minutes.

Surgical levels of anesthesia may be maintained with 0.5-3 percent enflurane. Maintenance concentrations should not exceed 3 percent. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of enflurane concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Analgesia: Enflurane 0.25 to 1.0 percent provides analgesia for vaginal delivery equal to that produced by 30 to 60 percent nitrous oxide. These concentrations normally do not produce amnesia. See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section.

Cesarean Section: Enflurane should ordinarily be administered in the concentration range of 0.5 to 1.0 percent to supplement other general anesthetics. See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section.

HOW SUPPLIED

ETHRANE (enflurane) is packaged in 125 and 250 ml amber-colored bottles.

Ethrane (enflurane) **10** years of experience confidence safety

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- Allays preoperative apprehension
- Leaves patients calm but cooperative
- Causes little, if any, IV irritation
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by most patients in clinical studies

Surgical procedures are perceived as frightening or unpleasant by most patients. If given the opportunity, many would rather not remember anything about the ordeal.

Ativan® Injection can help. Administered as recommended, Ativan Injection helps sedate the patient, relieves presurgical anxiety and diminishes recall of events surrounding surgery.

The dosage of Ativan Injection should be individualized for each patient. For those patients in whom a lack of recall and excellent sedation are desired, doses of 0.05 mg/kg up to a maximum of 4 mg should be administered. For patients in whom a lack of recall is not desired, as well as for the elderly or debilitated, the dose of Ativan Injection should be reduced.

See important information on following page.

Wyeth Laboratories
Philadelphia, PA 19101

ATIVAN® (LORAZEPAM) Ⓘ INJECTION IM or IV

ATIVAN® (LORAZEPAM) IV
INJECTION IM or IV

DESCRIPTION: Ativan* (lorazepam) Injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-$2H$-1,4-benzo-diazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal *failure*. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is given IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately post-injection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure.* Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure.* EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan* (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX* Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.
For IM or IV injection.
Protect from light. Keep in refrigerator.

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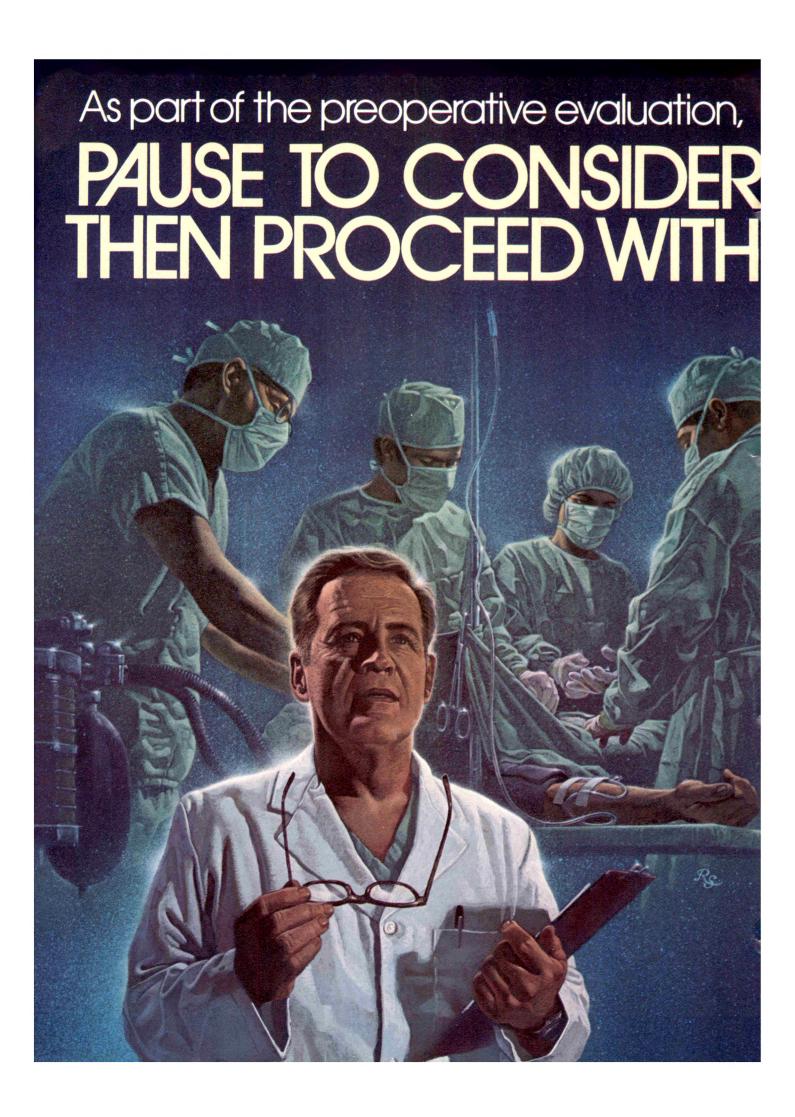
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ng/ml of Plasma — Hours after injection

Slightly depressed spontaneous respiration below 1.5 ng/ml; normal respiration below 0.7ng/ml.[1]

*Note: Respiratory depression may last longer than analgesic action and this risk increases with increasing doses.

1. McClain DA and Hug CC, Jr.: Intravenous fentanyl kinetics. *Clin Pharmacol Ther* 28(1):106-114, 1980.

Please see brief summary of Prescribing Information on next page.

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DESCRIPTION
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Warning: May be habit forming.
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CONTRAINDICATIONS
SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS
AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATION EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA. See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition. Where moderate or high doses are used (above 10 mcg./kg.), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received SUBLIMAZE (fentanyl). It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Drug Dependence—SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure—SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children—The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy—The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS
The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of SUBLIMAZE (fentanyl) are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol) hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol).

When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS
As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with *INAPSINE* (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION
50 mcg. = .05 mg. = 1 ml.
Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

I. *Premedication*—Premedication (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered *intramuscularly* 30 to 60 minutes prior to surgery.

II. *Adjunct to General Anesthesia*—See Dosage Range Chart

III. *Adjunct to Regional Anesthesia*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

IV. *Postoperatively (recovery room)*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usual Children's Dosage: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 20 to 30 mcg. (0.02 to 0.03 mg.)(0.4 to 0.6 ml.) per 20 to 25 pounds is recommended.

DOSAGE RANGE CHART

TOTAL DOSAGE

Low dose—2 mcg./kg. (.002 mg./kg.) (.04 ml./kg.) SUBLIMAZE* injection. Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period. *Maintenance:* Additional dosages of SUBLIMAZE* injection are infrequently needed in these minor procedures.

Moderate dose—2-20 mcg./kg. (.002-.02 mg./kg.)(.04-0.4 ml./kg.) SUBLIMAZE* injection. Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential. *Maintenance:* 25 to 100 mcg. (0.025 to 0.1 mg.)(0.5 to 2.0 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

High dose—20-50 mcg./kg. (.02-.05 mg./kg.)(0.4-1 ml./kg.) SUBLIMAZE* injection. During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20-50 mcg./kg. (.02-.05 mg./kg.)(0.4-1 ml.) of SUBLIMAZE* injection with nitrous oxide oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH, and prolactin.

When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression.

The main objective of this technique would be to produce "stress free" anesthesia. *Maintenance:* Maintenance dosage (ranging from 25 mcg. (.025 mg.)(0.5 ml.) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

As a General Anesthetic
When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg./kg. (.05 to 0.1 mg./kg.)(1 to 2 ml./kg.) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg./kg. (.15 mg./kg.)(3 ml./kg.) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

OVERDOSAGE
Manifestations: The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; and oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

HOW SUPPLIED
2 ml. and 5 ml. ampoules—packages of 10.
NDC 50458-030-02 NDC 50458-030-05

10 ml. and 20 ml. ampoules—packages of 5.
NDC 50458-030-10 NDC 50458-030-20
(For intravenous use by hospital personnel specifically trained in the use of narcotic analgesics).

March, 1980. Revised June, 1980. January, 1981
U.S. Patent No. 3, 164 600

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GENERAL MEETING INFORMATION

SCIENTIFIC PROGRAM:

The deadline for receipt of abstracts of papers for consideration by the Program Committee has passed. Abstracts which were submitted by the August 25, 1982 deadline date will be acknowledged by the Program Committee Chairman: E. Paul Didier, M.D., Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905.

SCIENTIFIC EXHIBITS:

The deadline for submitting scientific exhibit applications is December 31, 1982. Application forms are available from: B. B. Sankey, M.D., International Anesthesia Research Society, 3645 Warrensville Center Rd., Cleveland, Ohio 44122. Tel: (216) 295-1124.

TECHNICAL EXHIBITS:

Commercial firms may obtain application forms from the I.A.R.S. exhibit management company: Charles B. Slack, Inc., 6900 Grove Rd., Thorofare, New Jersey 08086. Tel: (609) 848-1000.

MEETING REGISTRATION MATERIAL:

Preliminary program, meeting registration and hotel reservation cards will be mailed in December 1982 to all I.A.R.S. members, associate members and educational members. Members residing outside of the U.S. who wish to attend the meeting should advise the I.A.R.S. Cleveland office by Deccember 1 so that registration material can be sent airmail.

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.... Preference will be given to new investigators.

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- -

The official application form for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

B. B. Sankey, M.D.
Executive Secretary
International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122, U.S.A.

Telephone: (216) 295-1124

Dissociation of Plasma and Cerebrospinal Fluid Beta-Endorphin-like Immunoactivity Levels during Pregnancy and Parturition

Richard A. Steinbrook, MD,* Daniel B. Carr, MD,† Sanjay Datta, MD,‡
J. Stephen Naulty, MD,* Carrie Lee, MD,§ and John Fisher, BS‖

STEINBROOK, R. A., CARR, D. B., DATTA, S., NAULTY, J. S., LEE, C., AND FISHER, J.: Dissociation of plasma and cerebrospinal fluid beta-endorphin-like immunoactivity levels during pregnancy and parturition. Anesth Analg 1982;61:893-7.

The association between central (cerebrospinal fluid [CSF]) and peripheral (plasma) levels of beta-endorphin-like immunoactivity (β-ELI) in nonpregnant women (n = 8) and pregnant women (a) at 16 to 20 weeks of gestation (n = 6), (b) at term (n = 21), and (c) in labor (n = 15) was investigated. Umbilical arterial (n = 11) and venous (n = 11) samples were also obtained. In agreement with previous investigations, it was found that plasma levels of β-ELI increased during labor (mean ± SEM: nonpregnant women, 63.5 ± 18.2; pregnant women at term, 64.0 ± 12.2; women in labor, 110.8 ± 30.3 pg/ml), and that levels of umbilical arterial plasma of β-ELI exceeded those in umbilical venous plasma (132.5 ± 34.0 versus 68.2 ± 22.2). However, CSF levels of β-ELI did not change over the course of pregnancy or during labor (nonpregnant women, 36.5 ± 15.8; pregnant women at 16 to 20 weeks of gestation, 60.1 ± 10.3; pregnant women at term, 57.5 ± 8.4; women in labor 48.5 ± 8.3 pg/ml). This evidence that plasma and CSF levels of β-ELI are dissociated during labor calls into question inferences regarding behavioral changes during parturition based on plasma β-ELI measurements.

Key Words: POLYPEPTIDES: endorphins; PREGNANCY: endorphins; ANESTHESIA: obstetric.

A NUMBER of investigators (1-7) have confirmed that plasma levels of beta-endorphin (β-EP) and its precursor, beta-lipotropin (β-LPH), increase in women during labor. Endorphins modulate the release of reproductive hormones such as gonadotro-

pins in humans (8) and animals (9), influence certain aspects of reproductive behavior in animals (10), and appear as well to underly the increase of pain threshold seen in pregnant animals (11). For these reasons, several researchers (2, 6, 7, 12) have proposed that the finding of elevated plasma levels of beta-endorphin-like immunoactivity (β-ELI, that is, β-EP + β-LPH) during labor in women may have relevance to explanations of the psychological responses during human pregnancy and parturition.

Concentrations of β-EP and β-LPH in plasma may have little or no correlation with those in brain or cerebrospinal fluid (CSF) (13, 14). Thus, it would appear more logical to correlate behavioral phenomena with central levels of these peptides, rather than with their values in peripheral blood. We sought to define the pattern of release of β-ELI into maternal CSF during successive stages of pregnancy and labor, and to determine the relationship between CSF and plasma levels of this material. We also assayed simultaneous samples of umbilical arterial and umbilical venous plasma for β-ELI to ascertain the relative fetal and placental contributions of this substance (15, 16).

Methods

Fifty healthy women provided informed consent for this study. The protocol was approved by the Human Subjects Committee of the Brigham and Women's Hospital.

Lumbar CSF (2 ml) and/or blood (10 ml) were obtained at the time of administration of spinal anesthesia in nonpregnant women undergoing minor gynecologic surgery (NP, n = 8) and in three groups of pregnant women: women at 16 to 20 weeks of gestation admitted for cervical circlage (C, n = 6), women having elective cesarean section at term (T, n = 21), and women at term in active labor for 6 to 8 hours (L, n = 15). In addition, simultaneous arterial and venous blood specimens (3 to 8 ml) were drawn from doubly clamped segments of umbilical cords of five infants delivered vaginally and of six delivered by elective cesarean section. In no instance had any woman received narcotics, oxytocics, or any medication other than antacids before sampling of blood or CSF.

Blood was collected in iced ethylenediaminetetraacetate (EDTA) tubes and immediately centrifuged at 0°C; plasma was frozen in the presence of 0.1 M N-ethyl maleimide as preservative. Plasma and CSF specimens were stored in polypropylene tubes at −70°C until blinded radioimmunoassay for β-ELI by published methods (17–19). In brief, individual aliquots of plasma and CSF were not all of sufficient volume to permit chromatography, and so total, unfractionated β-ELI was assayed using an antibody that recognized β-LPH and β-EP on an equimolar basis but that did not detect supraphysiologic amounts of alpha-endorphin, gamma-endorphin, leucine, or methionine enkephalin, or adrenocorticotropic hormone (ACTH). In each assay of plasma, all specimens and standard curves were run in duplicate and each assay tube contained 100 μl of plasma in a total incubation volume of 500 μl; in our hands this technique correlates well with analysis of extracted plasma specimens. For assays of CSF, both 100- and 200-μl sample aliquots were used, each in duplicate, and compared with a plasma-free standard curve. All assays were repeated at least once and the results computed by the log-logit method of Rodbard (20). It is of note that our human β-EP standards were analyzed by amino acid analysis, a method insensitive to adsorbed moisture. As peptides are hygroscopic, and crude preparations frequently contain 30% or more of gross weight as water, this refinement of "weighing" peptide in a fashion so as to exclude adsorbed water as an artifact typically results in calculated levels of β-ELI in unknown samples approximately 40% lower than if such precautions are not taken.

Statistical analysis of between-group differences was by Kruskal-Wallis one-way analysis of variance. Within-group comparison of plasma and CSF values were by Mann-Whitney U-test. Umbilical plasma values were analyzed by Student's t-test for paired samples and Spearman rank correlation (21).

Results

The differences in CSF levels of β-ELI (β-EP + β-LPH) between nonpregnant women and the three groups of pregnant subjects were not significant, although mean levels were slightly lower in the former group (Table 1). Plasma levels of β-ELI were the same in nonpregnant women as in patients at term before the onset of labor; however, after 6 to 8 hours of active labor, plasma levels of β-ELI increased 2-fold (Fig 1). The difference between plasma and CSF levels of β-ELI in women during labor was highly significant ($p < 0.01$).

Umbilical arterial levels of β-ELI exceeded those in umbilical vein in infants delivered by cesarean section without labor ($p < 0.025$), as well as in infants delivered vaginally ($p < 0.05$). There was good correlation between umbilical arterial and umbilical venous levels of β-ELI in both groups ($r_s = 0.89$ for cesarean section, $r_s = 0.70$ for vaginal delivery). Umbilical venous levels

TABLE 1

Beta-Endorphin-like Immunoactivity (β-EP + β-LPH) in Gynecologic and Obstetric Patients*

Group	Level of beta-endorphin in:			
	CSF	Plasma	Umbilical artery	Umbilical vein
		pg/ml		
Nonpregnant	36.5 ± 15.8	63.5 ± 18.2	—	—
Circlage (16–20 wk gestation)	60.1 ± 10.3	—	—	—
Elective cesarean	57.5 ± 8.4	64.0 ± 12.2	168.0 ± 46.5	65.7 ± 13.7
Active labor	48.5 ± 8.3	110.8 ± 30.3	89.6 ± 47.7	58.8 ± 47.3

* Values are means ± SEM.
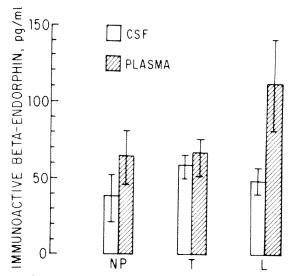
FIG 1. Plasma and CSF levels (mean ± SEM) of immunoactive beta-endorphin (i.e., beta-endorphin plus beta-lipotropin). Abbreviations are: NP, nonpregnant women; T, women at term pregnancy but not in labor; L, women in active labor. Plasma levels were significantly higher than CSF levels in women in active labor ($p < 0.01$).

of β-ELI correlated moderately well with maternal plasma levels in the group having elective cesarean section ($r_s = 0.60$), but there was no correlation in the group undergoing vaginal delivery ($r_s = 0.10$). Maternal plasma, umbilical arterial, and umbilical venous levels of β-ELI in six subjects having elective cesarean section are shown in Fig 2.

There was no correlation between Apgar scores and maternal or umbilical plasma levels of β-ELI.

Discussion

The present results for mean levels of β-ELI in plasma of pregnant women before and after the onset of active labor are of the same magnitude as values reported by other workers using unextracted assays using antibodies with equimolar affinity for β-EP and β-LPH (Table 2). Comparisons between our findings and those of workers using antibodies with lower affinity for β-LPH than β-EP are more problematic, because of the significant contribution of the former peptide to β-endorphin-like immunoactivity, but are also presented in Table 2, along with results derived from extracted plasma samples as well. Possible sources of disparity between our results and those of others include: first, we obtained specimens from patients only in operating or delivery rooms rather than in an ambulatory setting; second, we used standards prepared so as to exclude absorbed water as an artifact (a precaution rarely mentioned in the litera-

ture); third, we cannot exclude an altered ratio of β-EP to β-LPH during parturition, as our assay measured total β-endorphin-like immunoactivity, i.e., β-EP + β-LPH; and fourth, for the women in active labor, we timed our samples so as to coincide with access to CSF, i.e., somewhat before the time of delivery. It is likely that, had we delayed plasma sampling until the moment of delivery, the elevations in β-ELI might have been more pronounced (2, 5-7), but we chose to sample CSF and plasma simultaneously and the only time during active labor at which this could be accomplished ethically was upon insertion of the spinal needle.

Our finding of higher levels of β-ELI in umbilical artery than umbilical vein is in agreement with results of Wardlaw et al (3), but at variance with observations of Csontos et al (2), who found no difference in umbilical artery versus umbilical vein. The significant correlation we found between umbilical venous and maternal venous levels of β-ELI in women undergoing elective cesarean section but not during vaginal delivery confirms findings of Goland et al (6), who studied only the latter group and also failed to find a corre-
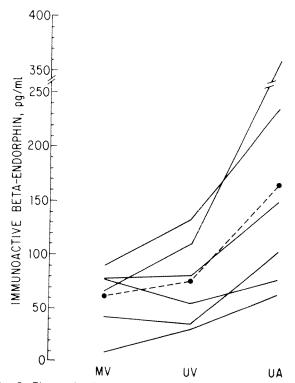
FIG 2. Plasma levels of immunoactive beta-endorphin (i.e., beta-endorphin plus beta-lipotropin) in samples from maternal vein (MV), umbilical vein (UV), and umbilical artery (UA) in six women whose babies were delivered by cesarean section without labor. Dashed line connects mean values. See text for statistical analysis.

TABLE 2

Beta-Endorphin-like Immunoactivity (β-EP + β-LPH) in Maternal Plasma: Published Values

Reference	Patients (n)*	Immunoactive β-endorphin†	β-LPH cross-reactivity	Comments
Akil et al (1)	"6 months to labor" (7)	62.5 ± 10 fmol/ml	10%–15% M	
Csontos et al (2)	First stage labor, active labor (11)	194 ± 58 pg/ml	Equimolar	Oxytocin given to all patients
	1st stage labor, "labor interval" (11)	129 ± 58 pg/ml		
	2nd stage labor, bearing down (11)	224 ± 58 pg/ml		
	2nd stage labor, "labor interval" (11)	228 ± 68 pg/ml		
	"Immediately" postpartum	456 ± 71 pg/ml		
Wilkes et al (4)	"At term" (6)	248 ± 28 pg/ml	2% by weight	
Fletcher et al (5)	Early 1st stage (9)	34 ± 10 pg/ml	Equimolar	
	Late 1st stage (8)	34 ± 10 pg/ml		
	2nd stage (3)	119 ± 78 pg/ml		
	Postpartum (9)	160 ± 82 pg/ml		
Goland et al (6)	Pregnant, not in labor (50)	15.6 ± 1.6 pg/ml	10.8% by weight	
	Early labor (9)	14.8 ± 2.3 pg/ml		
	Late labor (10)	70.3 ± 8.2 pg/ml		
	At vaginal delivery (26)	113 ± 13.3 pg/ml		
Kimball et al (7)	15–20 min after vaginal delivery (17)	159.4 ± 13.8 pg/ml	Equimolar	
	During cesarean section (6)	85.8 ± 16.5 pg/ml		
Budiamal et al (22)	During elective cesarean section (4)	544 ± 218 pg/ml	None	Samples chromatographed to remove β-LPH; CSF β-EP = 224 ± 35 pg/ml (cesarean) and 179 pg/ml (postpartum)
	Postpartum 1 hr (1)	264 pg/ml		

* Patients were without medications (or not stated to have received medications) except as noted.

† Values are means ± SEM. For purposes of tabulation, immunoactive β-EP results published as femtomoles per milliliter have been multiplied by 3.4 to convert to picograms per milliliter for studies in which β-LPH was measured equally with β-EP (references 2, 5, 22). Direct comparison of results of all assays is precluded by appreciable differences between studies in antibody affinities for β-LPH versus β-EP.

lation, and extends these findings by suggesting conjoint control of circulating β-ELI in mother and fetus at term, before the onset of labor. We did not confirm the speculation of Fletcher et al (5) that cord levels of β-ELI should correlate with Apgar scores, but we did not have sufficient numbers of depressed infants to test their hypothesis adequately, as only one of the infants in whom we measured umbilical arterial and venous levels had an Apgar score <8 at both 1 and 5 minutes. Our finding that umbilical arterial levels of β-ELI exceed umbilical venous levels is compatible with fetal pituitary production of β-ELI (2), but placental manufacture, or possible placental degradation, cannot be excluded. Indeed, the concentration of β-ELI has been found to increase in placental tissue following delivery (7), so that further studies are needed to clarify the factors influencing fetal and placental contributions to umbilical cord levels of β-ELI.

Finally, the present study provides evidence that,

during labor, plasma and CSF levels of β-ELI are dissociated. A preliminary report by Budiamal et al (22), examining levels of β-EP in four women before elective cesarean section and one woman 1 hour after delivery by an unspecified route, also reported no correlation between levels of β-EP in plasma and CSF. However, in that preliminary account, plasma levels of β-EP in the four women about to have elective cesarean sections averaged twice as high as simultaneous values in CSF (a result at variance with ours), absolute concentrations of β-EP in plasma and CSF were strikingly higher than in our series or in most other published accounts, and no subjects were studied during active labor. Nonetheless, our results lend support to their conclusion that "an explanation for the markedly elevated plasma β-EP without corresponding rises of spinal fluid β-EP levels may be that the β-EP of plasma and CSF are produced at different locations and have different physiological functions" (22).

The pattern of dissociation between plasma and CSF levels of β-ELI that we observed, namely, an increase in plasma concentration with no change in CSF values, bears striking similarity to that displayed by endorphins and other pituitary hormones in response to other forms of physiologic stress in animal models (23, 24) but not previously examined during active labor. This finding suggests that the occurrence of elevated peripheral β-ELI levels in labor may be a nonspecific response to stress rather than a specific concomitant of parturition, and may explain Fletcher's failure to correlate plasma β-ELI with simultaneous pain scores during labor (5), but of course cannot rule out a delayed increase in CSF β-ELI or a localized increase of β-ELI in a brain region not reflected in lumbar CSF concentrations.

We conclude that maternal CSF levels of beta-endorphin-like immunoactivity do not change over the course of pregnancy and labor, whereas maternal plasma levels increase with labor. Consequently, inferences regarding behavioral changes in parturition based on plasma β-ELI measurements must be reexamined.

Umbilical arterial levels of β-ELI exceed those in umbilical veins, consistent with fetal production of β-ELI. The physiologic role of fetal β-endorphin remains to be determined.

ACKNOWLEDGMENTS

ADDENDUM

A recent report by T. A. Thomas, J. E. Fletcher, and R. G. Hill (Br J Anaesth 1982;54:401-8) provides evidence suggesting a relationship between analgesic drugs and the increase in plasma β-ELI that accompanies labor.

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Effects of Enflurane on Brainstem Auditory Evoked Responses in Humans

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DUBOIS, M. Y., SATO, S., CHASSY, J., AND MACNAMARA, T. E.: Effects of enflurane on brainstem auditory evoked responses in humans. Anesth Analg 1982;61:898-902.

The effects of enflurane anesthesia on brainstem auditory evoked responses (BAERs) was determined in 10 patients with normal hearing undergoing various surgical procedures. Arterial blood pressure, body temperature, and arterial P_{CO_2} were controlled during the 2- to 5-hour recording sessions. End-tidal enflurane concentrations were continuously recorded on a Chemetron Medspect II mass spectrometer in three subjects. BAERs were obtained by, and recorded on, a Nicolet CA 1000, from C2 with reference to A1 or A2, with a 2000 click-averaging for each measurement. Enflurane administered at clinical concentrations (0.5% to 3%) produced consistent changes in BAER latencies. The waves significantly affected ($p < 0.01$) were waves III, IV, and V and interpeak latency I-V. The magnitude of these changes was related to the concentration of enflurane and was magnified by temporarily decreasing the Pa_{CO_2}. These findings confirm similar data obtained in animals which have shown the same effects at doses that can produce generalized seizure activity. BAER analysis shows that changes predominate at the pons and midbrain levels and affect the brainstem conduction time, which likely reflects the action of enflurane on the activity of the reticular activating system.

Key Words: BRAIN: evoked responses; ANESTHETICS, Volatile: enflurane.

BRAINSTEM auditory evoked response (BAER) recording represents a relatively new noninvasive way of assessing the effects of diseases (1) or drugs (2) on the brainstem function. In 1970 Jewett et al (3) reported recording small potentials on the scalp during the first 7 msec following auditory stimulation, a "far-field" recording of brainstem activity (1). A click stimulus presented to the ear evokes reproducible and typical responses on the scalp with up to seven wave components. Each of these waves has been related to specific regions of the auditory pathway, from the acoustic nerve (wave I) to the thalamus

and thalamocortical radiations (waves VI and VII), whereas the waves II to V represent different nuclei of the brainstem. Since the findings of Jewett and coworkers (3), there have been many reports linking abnormalities in these wave potentials with specific lesions of the deep subcortical auditory pathway (4).

One major property of BAERs is that, unlike spontaneous electroencephalogram (EEG) or responses to long latency evoked responses, they are apparently insensitive to centrally acting drugs including anticonvulsants, tranquilizers (2), and anesthetics such as halothane (5) or barbiturates, even when spontaneous EEG activity is abolished (2). However, reports in animals (6) have shown that enflurane may modify BAERs. Single or multiple unit recordings and regular EEG recordings at various levels of the central nervous system (7) have all outlined the unique depressant (on the brainstem) or excitatory (on the cortex) effects of enflurane on neuronal activity, leading to cortical epilepsy. Electrographic epileptiform discharges are not uncommonly observed during the administration of clinical concentrations (2% to 3%) of enflurane, especially in the presence of hypocapnia (8).

In the present study, the effects of various concentrations of enflurane on BAERs latency and amplitude

have been assessed in surgical patients. The correlation between possible BAER abnormalities and development of enflurane-induced epileptiform activity was also examined, together with the potential neurophysiologic implications of such findings.

Methods and Materials

BAER recordings were carried out in 10 patients undergoing various surgical procedures who agreed to participate in the study (age range: 21 to 59 years, six women and four men). All were A.S.A. class I or II physical status, with no cardiovascular, renal, pulmonary, or neurologic pathology; all had normal hearing. After pentobarbital premedication, general anesthesia was induced with thiopental and maintained with pancuronium, enflurane, and oxygen, for the 2- to 4-hour duration of the surgery. Arterial blood pressure and body temperature were maintained within preanesthetic control values (maximum esophageal temperature variation was $\pm 1°C$ control value). Arterial P_{CO_2} was also maintained between 32 and 40 mm Hg, except for a few short occasions (10 to 15 minutes) when hyperventilation decreased Pa_{CO_2} to between 25 and 30 mm Hg. A Chemetron Medspect II mass spectrometer was used in three subjects to measure and record on-line end-tidal (i.e., alveolar) enflurane and CO_2 concentrations.

BAER was obtained in a conventional way from gold cup electrodes placed on Cz (midline-central vertex in the 10–20 electrode system), with reference to A1 or A2, namely right or left ear lobes. When the right ear was stimulated the responses were obtained from the channel connecting Cz and A2. The ground electrode was placed at Fz position (midline-midfrontal in the 10–20 system). Before testing, hearing threshold to 11 Hz clicks (generated by a Nicolet noise masking unit 1007A) was determined for each patient. The testing intensity of stimulating clicks—administered through headphones—was set 70 dB above the hearing level and the masking noise to the contralateral ear 40 dB above the hearing level. Using Nicolet CA 1000, 2000 clicks were averaged with analysis time of 10 msec. The responses were immediately transferred to paper with XY plotter, and positive peak latencies were measured with cursors on the averager. It took 4 to 5 minutes to obtain one set of responses and the same procedure was repeated as soon as the previous set was secured. The EEG signal was amplified 10,000 times (Nicolet preamplifier) and then led to the averager's amplifiers with a sensitivity setting of ± 10 μV.

The day before testing, all patients had a control

recording. Based on the clarity of responses obtained during pretesting, the ear to be stimulated during testing was selected. On the day of surgery, using exactly the same technique, a continuous recording was carried out beginning immediately before anesthetic induction and lasting until awakening. According to the length of the surgery, the total number of BAER recordings obtained at different anesthetic concentrations of enflurane varied from 20 to 60. Only BAERs recorded after 15 minutes of constant enflurane concentration (or whenever end-tidal enflurane concentration appeared stable on the mass spectrometer) were retained for analysis, assuming that at that time blood-brain equilibrium of the drug had been achieved. In addition to visual analysis of individual tracings, statistical analysis was carried out on individual BAER latencies within patients and between clinical conditions, i.e., comparison of the values obtained at different enflurane concentrations using Student's t-test for paired data. The clinical conditions tested were: control (previous day); after induction (2 to 5 minutes after thiopental injection); during 3%, 2%, and 1% enflurane; and after enflurane was discontinued at the end of the procedure.

Results

All mean BAER latency findings are summarized in the Table. After thiopental induction, no significant changes were found. Enflurane, on the other hand, consistently produced changes in BAER latencies. The waves most affected were waves III, IV, and V; these were statistically significant from the control values with 2% and 3% (for waves III, IV, and V) and with 1% (for wave V) enflurane. The magnitude of the delay in latency was directly related to the concentration of enflurane, being maximum with the highest concentration (3%) and reversing itself, although incompletely, as the concentration decreased. A representative BAER recorded from one subject is shown in Fig 1. When end-tidal enflurane was recorded by mass spectrometry, the same trend between latencies and alveolar concentrations was observed (Fig 2). Interpeak latencies (IPL) were also affected (see Table). A statistically significant increase was found for IPL III-V with 2% (0.25 msec) and 3% (0.3 msec) enflurane. IPL I-V demonstrated an even more substantial increase (0.39 msec) with 3% enflurane, which remained significant at 2%. IPLs, however, were not statistically significantly different from control values during administration of 1% enflurane or when the patient was awakening, although mean values remained elevated.

TABLE

Latencies and Interpeak Latencies of Brainstem Auditory Evoked Responses for Different Clinical Conditions*

	Control	After pentothal	3% Ethrane†	2% Ethrane†	1% Ethrane†	Ethrane off
Latencies						
I	1.58 ± 0.02	1.60 ± 0.04	1.67 ± 0.04	1.66 ± 0.04	1.68 ± 0.05	1.54 ± 0.05
II	2.69 ± 0.05	2.64 ± 0.07	2.75 ± 0.06	2.75 ± 0.06	2.78 ± 0.08	2.69 ± 0.08
III	3.65 ± 0.08	3.59 ± 0.09	3.81 ± 0.12‡	3.77 ± 0.10‡	3.72 ± 0.13	3.66 ± 0.09
IV	4.65 ± 0.08	4.63 ± 0.12	4.91 ± 0.13‡	4.90 ± 0.10‡	4.78 ± 0.16	4.65 ± 0.08
V	5.57 ± 0.07	5.63 ± 0.06	6.04 ± 0.06‡	6.00 ± 0.06‡	5.89 ± 0.08‡	5.78 ± 0.07
Interpeak latencies						
I–III	2.05 ± 0.09	1.99 ± 0.10	2.14 ± 0.15	2.11 ± 0.14	2.04 ± 0.16	2.10 ± 0.11
III–V	1.93 ± 0.06	2.04 ± 0.07	2.23 ± 0.09‡	2.18 ± 0.05‡	2.17 ± 0.09	2.12 ± 0.07
I–V	3.99 ± 0.07	4.03 ± 0.06	4.38 ± 0.09‡	4.31 ± 0.11‡	4.21 ± 0.11	4.22 ± 0.07

* Values are means ± SEM.
† Inspired concentration.
‡ Significant at 0.01 level or less, t-test for paired data with reference to control values, two-tailed.
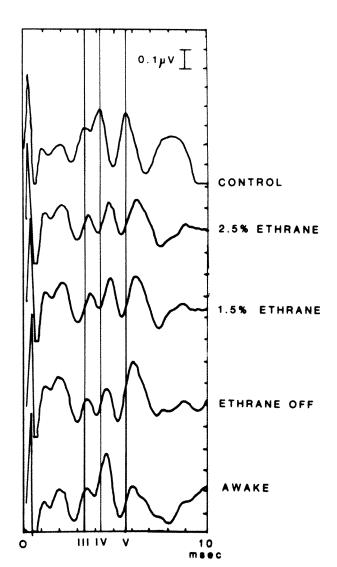
FIG 1. BAER recording obtained in one patient at different enflurane inspired concentrations.

FIG 2. Relationship between end-tidal enflurane concentration (measured and recorded on Chemetron Medspect II mass spectrometer) and BAER latencies. Lower trace is end-tidal P_{CO_2}.

Amplitudes of BAER waves failed to demonstrate consistent changes; occasionally, in four subjects, waves III, IV, and V decreased during 3% enflurane, but these changes were not statistically significant. When hyperventilation was instituted for 10 to 15 minutes, further delays in latencies were observed, again in waves III, IV, and V, which were directly related to the lower Pa_{CO_2} (Fig 3).

Discussion

The recording arrangements used in this study were based on a standard, widely accepted technique, and the normative data obtained in our laboratory are comparable to those obtained in other laboratories (9). In addition to the stimulus characteristics, body
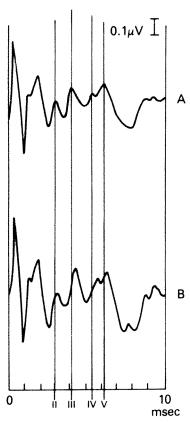
FIG 3. BAER traces in same patient and at same enflurane inspired concentration (3%) with normoventilation (A) and hyperventilation (P_{CO_2} = 27 mm Hg) (B).

temperature, age, and sex of the subjects tested can cause much of the variability in BAER normally encountered (10).

In our study, body temperature was controlled and in previous work no significant difference in BAER has been reported in the age range of our patients. Although we had a slightly unequal sex ratio (6:4) and although BAER IPL are 0.1 to 0.2 msec faster in women than in men (10), this did not significantly affect our results as statistical analyses used individuals as their own controls and did not refer to a separate control group.

No significant changes in BAER latencies were recorded after thiopental induction, confirming the previous finding that BAERs are insensitive to barbiturates (2, 5), even when obvious changes in spontaneous EEG are recorded. It has been shown (11) that lesions of the cortex or of the thalamus are not associated with changes in BAER. However, enflurane consistently delayed BAER, mainly affecting components III, IV, and V. Although the precise origin of BAER neural generators in the brainstem remains uncertain and may probably be multiple (12), a con-

sensus exists (4, 9) relating the vertex-positive components III and IV to the pons (superior olivary complex and lateral lemniscus) and V to the midbrain. We conclude therefore that enflurane, unlike thiopental, has an action in those brainstem locations.

Although delays in BAER latency were observed for most of the enflurane concentrations we studied, they were only statistically significant at higher concentrations (2% and 3%) and when hypocapnia was also present. These conditions (high enflurane concentration and hypocapnia) are the factors that produce generalized EEG spike-wave activity (8). It has been shown in cats (13) that concentrations of enflurane that trigger seizure activity significantly prolong the BAER components generated in the rostral brainstem. These seizure discharges are known to be potentiated when the midbrain reticular formation tonic neuronal activity is further depressed [e.g., by local cooling (14)]. Enflurane itself has such a depressant effect (7, 15), which may account for the epileptogenicity of this anesthetic. The relationship of enflurane seizure activity and BAER latency at different levels of Pa_{CO_2} has also been demonstrated (16), and the anecdotal finding of our study showing BAER latency delay with low Pa_{CO_2} levels further illustrates the correlation between BAER changes and seizure activity with enflurane.

IPLs are usually considered to be more representative of pathologic changes than are individual absolute latencies because they are relatively independent of variables such as hearing impairment or click intensity (12). IPL I-V is defined as brainstem conduction time and values at or greater than 4.4 msec are considered abnormal (12). Such values have often been obtained in our study during exposure to 3% enflurane. Such an increase in neuronal conduction at brainstem level has not to date been found with other anesthetics and has only been reproduced by using pentylenetetrazol in the monkey in doses producing petit mal epilepsy (13).

In conclusion, our study confirms the fact that BAER recording represents a relatively simple, non-invasive method for monitoring neuronal function at brainstem level and for testing the functional integrity of brainstem function when using pharmacologic agents. The study also demonstrates that in man there are definite changes in BAER latencies and IPLs when enflurane is administered and that these changes should be taken into consideration when BAERs are recorded in neurosurgical situations. The abnormalities found are suggestive of a maximal effect on the midbrain reticular formation and correlate with the

development of enflurane-induced epileptiform EEG activity. The significance of these findings is 2-fold: they confirm the hypothesis, expressed by some authors (14), of the rostral brainstem playing a role in the mechanism of generalized seizure activity (13) in a type of epilepsy sometimes called "corticoreticular" (14), and they also demonstrate a neurophysiologic action of enflurane which is apparently unique among general anesthetics.

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Etiologic Factors in Neuropsychiatric Complications Associated with Cardiopulmonary Bypass

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A prospective study of 204 patients undergoing operations requiring cardiopulmonary bypass was undertaken to determine the incidence and etiologic factors leading to postperfusion cerebral dysfunction and to determine whether pretreatment with thiopental, 15 mg/kg, would reduce the incidence. Patients were randomly assigned to a control (diazepam) or study (thiopental) group and were treated identically except for the drug administered. Patients were examined neurologically on the 1st and 4th postoperative day and a psychometric test was administered on the 4th day. Although fewer neuropsychiatric complications were present in patients given thiopental, the difference was not significant. The overall incidence of cerebral dysfunction attributable to cardiopulmonary bypass alone was 16.2% for transient and 6.4% for persistent dysfunction (present at the 10th postoperative day). The incidence of postoperative cerebral dysfunction was more than twice as high in patients undergoing intracardiac than in patients having extracardiac operations and more than 4 times as high in patients more than 60 years of age than in younger patients. Perfusion pressure less than 50 torr with hematocrit less than 30% was not related to development of postoperative cerebral dysfunction. The data suggest that air or particulate emboli originating within the heart or aorta are the major causes of postbypass cerebral dysfunction.

Key Words: ANESTHETICS, Intravenous: thiopental; BRAIN: thiopental protection; COMPLICATIONS: neuropsychiatric; SURGERY: cardiovascular.

ALTHOUGH refinements in apparatus and techniques have substantially reduced morbidity related to cardiopulmonary bypass, unpredictable major and minor central nervous system complications continue to occur. The reported incidence of neurologic and/or psychiatric complications following operations requiring extracorporeal circulation ranges from 7% to 44% for transient and from 1.6% to 23% for permanent complications (1-3). Preexisting cerebrovascular disease, increasing age, and duration of bypass have been suggested as predisposing factors and air or particulate emboli and hypotension have been proposed as precipitating causes. Attempts to reduce the incidence by arterial line filters (4-7), high

perfusion pressures (8-11), and treatment of carotid occlusive disease (12) have had limited or equivocal success.

In view of the uncertainty of both the incidence and etiology of this complication, a prospective study with two major objectives was undertaken. The first was to gain new insights into predisposing and precipitating causes of neuropsychiatric complications of cardiopulmonary bypass. The second was to investigate the possibility that a clinical dose of thiopental might reduce the incidence of these complications regardless of etiology. Pretreatment of animals with large doses of thiopental increases the tolerance of the brain to global hypoxemia (13) and reduces infarct size after occlusion of a cerebral artery (14). No studies in man have been attempted to demonstrate a similar cerebral protective effect of pretreatment with thiopental. We hoped the cerebral complications following cardiopulmonary bypass in man would provide a suitable model for demonstrating this effect of thiopental. Complications were assessed by both physical examination and psychometric testing and, by design of the study, causes of complications other than the use of an extracorporeal circuit were eliminated.

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Methods

Adult patients without neurologic or psychiatric illness on routine history and physical examination and scheduled for operations requiring cardiopulmonary bypass were studied. Patients fulfilling these criteria were randomly assigned by day of week and order of operation within days to a study group that received thiopental or to a control group that received diazepam. Both anesthetic techniques had been routinely used previously in the management of our patients.

Patients in the study group were given 6 mg/kg of thiopental for induction of anesthesia and additional increments of 100 to 200 mg after induction until at least 15 mg/kg had been administered before cardiopulmonary bypass, a period of approximately 45 minutes. The rate of administration of thiopental was governed primarily by the hemodynamic response to thiopental. Although the bifrontal electroencephalogram (EEG) was monitored, a specific and uniform degree of suppression could not be maintained in all patients. Transient complete EEG suppression and burst suppression were usually observed after administration of the last one or two increments of thiopental. Control patients received diazepam, 0.15 mg/kg, during induction without additional doses of this drug. In addition, during induction all patients in the study were given morphine, 1 mg/kg, or fentanyl, 15 μg/kg, pancuronium, 150 μg/kg, and nitrous oxide by inhalation. In 80% of the patients in both groups halothane or enflurane was added to nitrous oxide at some period during operation to control hypertension.

Surgical Management

Bubble oxygenators of various types were used (Travenol, Rygg, Harvey, Cobe, and Bentley). In addition to the filters built into each oxygenator, a 40-μ depth filter was used in the cardiotomy return line. No filter was used in the arterial line. Patients received heparin, 300 units/kg, before cannulation and oxygenators were primed only with 20 ml/kg of 5% dextrose in lactated Ringer's solution to which heparin, 2000 units/L, was added. During bypass perfusion flow was maintained between 40 and 60 ml/kg/min as determined by venous return. Patients' nasopharyngeal temperatures were maintained greater than 35°C by a heat exchanger. Hematocrit during perfusion ranged from 18% to 30%.

All operations were performed through a median sternotomy. During procedures requiring atriotomy or ventriculotomy, a cannula was placed in the right

superior pulmonary vein for venting. Air was aspirated by needle and syringe from the left ventricle and ascending aorta before terminating cardiopulmonary bypass. In myocardial revascularization operations (coronary artery bypass, CAB) the heart was vented through a continuous suction cannula in the proximal aorta. Cardiopulmonary bypass was not discontinued until adequate cardiac function had been established. Any patient who required continuous pharmacologic support or intra-aortic balloon counterpulsation to permit weaning from bypass or who experienced marked hypotension (systolic blood pressure less than 80 torr for more than 3 minutes) in the prebypass or postbypass period was excluded from the study. Cerebral electrical activity was monitored for global ischemia during bypass. No patient included in the study had absent EEG activity during any period of the operation except in response to increments of thiopental.

Study Plan

Data recorded during cardiopulmonary bypass for correlation with outcome included lowest perfusion pressure and its duration, duration of mean perfusion pressure below 50 torr, and duration of bypass. Blood pressure was recorded directly from the radial artery. Within 24 hours after operation, a preliminary neuropsychiatric evaluation was made. All evaluations were made by one medical student employed for this purpose after a preliminary 2-week training and practice period. All positive findings reported by him were confirmed by one investigator (S.S.). Neurologic testing included: (a) movement against resistance of all extremities in response to command; (b) presence of triceps, biceps, knee, and ankle reflexes; and (c) the plantar reflex response. Psychiatric evaluation included orientation to time, place, and person and presence of any gross delusional or irrational behavior.

On the 4th postoperative day a more detailed neuropsychiatric examination included: (a) testing strength of all upper and lower extremity motor groups; (b) sensory perception of sharp-dull, hot-cold in all spinal nerve distributions; (c) evaluation of motor and sensory function of cranial nerves (d) presence of spinal, cranial, and plantar reflexes, and (e) observation of coordination and gait. Psychiatric evaluation included: (a) orientation; (b) eating and sleeping pattern; (c) perception of the attitude toward postoperative status; (d) atypical behavioral patterns such as aggressiveness, hostility, withdrawal, delusions, or hallucinations.

At the end of the clinical examination on the 4th day the Trail Making Test devised by Reitan was administered. (The test forms and a manual of instruction can be purchased from R. M. Reitan, Neuropsychology Laboratory, 2205 East Greenlee Road, Tucson, AZ 85719.) We anticipated that this test, which is highly sensitive to the presence of organic brain damage, would provide a more sensitive measure than the clinical examination. This two-part psychometric test asks the patient to connect a series of circles numbered sequentially from 1 to 25 (part A) and to connect a series of 25 circles both numbered and lettered sequentially; i.e., 1 to A to 2 to B to 3 . . . (part B). The test is scored in seconds required to complete the task. In Reitan's original work with 200 organically brain-damaged patients and 84 control subjects, a cut-off score of 50 seconds in part A correctly identified 70% of brain-damaged patients with only 5% false-positive readings among control subjects. A cut-off score of 100 seconds in part B correctly identified 83% of brain-damaged patients with 12% false-positive readings among the control patients (15). These cut-off scores for normality were used in analysis of our data.

Based on the neuropsychiatric examination alone, certain minimal criteria were established for the diagnosis of cerebral dysfunction in order to decrease false-positive readings which might result from persistent drug effects, peripheral neuropathies, etc. A neurologic abnormality was considered present only when at least two complementary reflex, sensory, or motor abnormalities were found, e.g., weakness of a leg with extensor plantar reflex on the same side. On the 4th postoperative day generalized discoordination with or without focal signs was also considered an abnormality. To eliminate "ICU psychosis," a psychiatric abnormality was considered present when it developed within 48 hours of surgery and/or persisted for more than 48 hours after discharge from the intensive care unit. For the purpose of this study, abnormalities were considered transient if they disappeared by the 10th postoperative day and persistent if they were present even though improving at the 10th postoperative day.

Statistical testing of relative frequencies of complications was by chi-square corrected for continuity and for quantitative data by the one-tailed Student's t-test for unpaired data. Values are expressed as means ± SD.

Results

Characteristics of the 204 patients included in the study and control groups are shown in Table 1. The groups were not significantly different with regard to any characteristic listed.

Based on neuropsychiatric examination only, the incidence of cerebral dysfunction following cardiopulmonary bypass was 16.2% for transient and 6.4% for persistent abnormalities (Table 2). Operations requiring opening of a cardiac chamber, e.g., valve replacement or ventricular aneurysm, were followed by more than twice the incidence of both transient and persistent dysfunction. Neurologic abnormalities occurred in 14 patients, including the eight patients with combined neurologic and psychiatric abnormalities, see Table 3. Of the four patients with focal sensory abnormalities, two had hypesthesia over an ipsilateral arm and leg and two had unilateral sensorineural hearing loss. One patient with hearing loss also had ipsilateral facial hypesthesia. Of five patients with focal motor abnormalities, one h·d ptosis of one eyelid with absent reflexes in the ipsilateral arm and leg, one had tongue deviation on protrusion associated with absent limb reflexes on one side, and three had hemiparesis. Of the nine patients with focal sensory or motor loss, only two (one with unilateral hypes-

TABLE 1

Patient Characteristics

	Thiopental	Diazepam
No. of patients	110	94
Coronary bypass	79%	77%
Open ventricle	21%	23%
Sex (M/F)	91%/9%	83%/17%
Mean age (yr)	55.0	54.6
Age ≥ 60 yr	31%	30%
Preoperative hypertension	25%	31%
Diabetes	5%	2%

TABLE 2

Neurologic and Psychiatric Abnormalities in 204 Postoperative Patients*

	Neurologic only	Both neurologic and psychiatric	Psychiatric only	All abnormal patients
Coronary artery bypass (n = 159)	6/3	3/2	11/2	12.6%/4.4%
Open ventricle (n = 45)	0/0	5/4	8/2	28.9%†/ 13.3%‡
All patients (n = 204)	6/3	8/6	19/4	16.2%/6.4%

* Values are ratios indicating transient/persistent.
† Significantly greater than CAB, p < 0.005.
‡ Significantly greater than CAB, p < 0.025.

TABLE 3

Neurologic Abnormalities in 14 Postoperative Patients

	Transient	Persistent	Total
Generalized discoordination alone	0	2	2
Generalized discoordination and extensor plantar reflex	3	0	3
Focal sensory abnormality	1	3	4
Focal motor abnormality	1	4	5
Total	5	9	14

thesia and one with eyelid ptosis) returned completely to normal by the 10th day.

The psychiatric abnormalities of 27 patients (19 with psychiatric alone and eight with combined neurologic and psychiatric abnormalities) are shown in Table 4. Grossly atypical behavior patterns were observed in 12 patients. In addition to abnormal behavior, 13 patients were disoriented as to two or more references (time, place, and person) and two were frankly psychotic. In one, the psychosis consisted of religious hallucinations and in the other disorganized hallucinations and delusions of threatening actions by medical personnel. These were transient in both patients.

Eight of the 14 patients with neurologic abnormalities and 21 of the 27 with psychiatric abnormalities were identified on the 1st postoperative day. In only two patients, both with neurologic abnormalities, did the dysfunction disappear between the examinations on the 1st and 4th days.

Both part A and part B of the Trail Making Test clearly confirmed the existence of two distinct populations. Patients without clinical evidence of cerebral dysfunction required 35.2 ± 8.7 seconds to complete part A compared with 64.2 ± 28.0 seconds for 32 of the 33 patients with clinical evidence of dysfunction ($p < 0.005$). One patient was unable to perform the test. Assuming 50 seconds as the upper limit of normal for part A, only 7% (12/168) of clinically normal patients exceeded 50 seconds (Fig 1). Responses to part B were more sensitive. Mean time for completion of part B by clinically normal patients was 89.2 ± 16.4 seconds compared with 169 ± 59.8 seconds for those clinically abnormal ($p < 0.005$). Twenty-five percent (42/168) of clinically normal patients required more than 100 seconds in part B, whereas no clinically abnormal patients could perform the task in less than 100 seconds (Fig 2).

Data were analyzed in two ways for factors that predispose to or prevent postperfusion cerebral dysfunction. In one analysis, the presence of cerebral

dysfunction was based on clinical examination only. In the other, incidence of clinically diagnosed dysfunction and/or abnormal Trail Making Test score was considered cerebral dysfunction. Factors that were significantly related using one measure were significantly related using the combined measure and vice versa.

The administration of thiopental did not alter the incidence of transient cerebral dysfunction or its persistence in either open ventricle or closed ventricle or combined groups (Table 5). Although the incidence of dysfunction was lower in both these groups when given thiopental, the differences were not significant. Neither duration of cardiopulmonary bypass nor perfusion pressure less than 50 torr correlated with cerebral dysfunction (Table 6). The incidence of neuropsychiatric dysfunction in patients 60 years of age or

TABLE 4

Psychiatric Abnormalities in 27 Postoperative Patients

	Transient	Persistent	Total
Insomnia, anorexia, depression hostility, combativeness	10	2	12
Above plus disorientation	6	7	13
Above plus hallucinations or delusions	2	0	2
Total	18	9	27
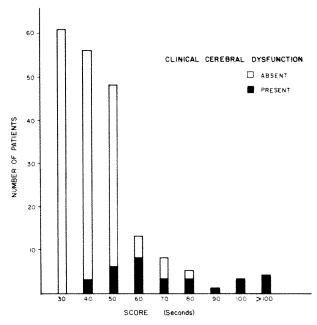
FIG 1. Distribution of scores in part A of Trail Making Test of Reitan (15). See text for description. Normal score is 50 seconds. Only 7% of clinically normal patients exceeded 50 seconds, but 28% of clinically abnormal patients completed test in less than 50 seconds.

CLINICAL CEREBRAL DYSFUNCTION

□ ABSENT
■ PRESENT
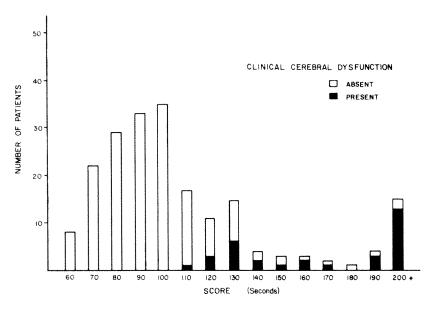
FIG 2. Distribution of scores in part B of Trail Making Test of Reitan (15). See text for description. Normal score is 100 seconds; no patient who was clinically abnormal at time of testing performed test in less than 100 seconds; however, 25% of clinically normal patients required more than 100 seconds.

TABLE 5

Influence of Thiopental on Occurrence and Persistence of Postoperative Cerebral Dysfunction

	No. of pa-tients	Patients with cerebral dysfunction		Abnormal patients (total/ persistent)
		Total	Persis-tent	
Coronary artery bypass only				
Thiopental	87	8	4	9.2%/4.6%
Diazepam	72	12	3	16.7%/4.2%
Open ventricle				
Thiopental	23	6	2	26.1%/8.7%
Diazepam	22	7	4	31.8%/18.2%
All operations				
Thiopental	110	14	6	12.7%/5.5%
Diazepam	94	19	7	20.2%/7.5%

older was significantly higher than in younger patients (35% of 62 patients versus 8% of 142 patients, $p < 0.005$). Although the number of women in this study was small, cerebral dysfunction occurred significantly more frequently in women (31% of 26 patients) than in men (14% of 178 patients) ($p < 0.05$).

Although 13 patients were considered for the purpose of this study to have persisting dysfunction at the 10th postoperative day, most were recovering rapidly at this time. Only five patients, three with hemiparesis and two with mild psychiatric disturbances, were only slightly improved by the 10th day.

Discussion

An increasing body of experimental evidence in animals suggests that the use of anesthetic doses of thiopental administered before, during, or shortly after a cerebral insult can prevent or diminish irreversible brain damage. Protection is greatest when thiopental is administered before the insult and its efficacy decreases with time of administration after the insult (16). In dogs, thiopental pretreatment reduced the clinical and chemical cerebral derangements produced by profound hemorrhagic hypotension (13) and reduced infarct size, mortality, and neurologic deficit after surgically induced focal cerebral vascular occlusion (14, 17). This protective effect was attributed to the reduced oxygen requirement of cerebral tissue functionally depressed by thiopental as protection is maximal at doses producing EEG silence (18, 19) and as only anesthesia-inducing stereoisomers of barbiturates are effective (20).

Experiments designed to demonstrate a cerebral protective effect of thiopental in man have as yet been unsuccessful and are limited to administration of thiopental after a cerebral insult. The similarity of the cerebral insults associated with cardiopulmonary bypass (hypotension and emboli) and the animal studies showing protection, especially with pretreatment, suggested the present study as an appropriate model for evaluation of whether thiopental might similarly reduce neurologic complications in humans exposed to possible cerebral ischemic insults. Use of diazepam in our control patients is supported by failure of diazepam to protect the brain against ischemic insults or to reduce cerebral metabolism in either clinical and

experimental situations (20, 21). None of the other anesthetics used in this investigation have been shown to protect against cerebral ischemia. Despite this, thiopental did not appreciably reduce the incidence or severity of cerebral complications in this model.

Our study design possessed limitations that could account for our failure to demonstrate protection. Because thiopental is a negative inotropic agent, a uniform dose over a specific time interval could not be administered to all patients in this population and the total dose was limited. For the same reason a uniform degree of EEG suppression and, by inference, a uniform degree of suppression of cerebral metabolic oxygen utilization could not be induced. Based on the pharmacokinetics of bolus administration of thiopental, at least 10% of peak brain concentration was present between 1 and 2 hours after administration and was operative during the period of cardiopul-

monary bypass (22). No available data relate this dose to degree of brain metabolic suppression. Although larger doses of thiopental might prove to be protective of cerebral ischemic insults associated with cardio-pulmonary bypass, this potential cannot be realized in clinical practice because of simultaneous adverse effects on cardiovascular function in man, especially those with cardiovascular disease severe enough to necessitate operations performed under cardiopulmonary bypass.

Based on reports of neurologic sequelae following operations requiring cardiopulmonary bypass during the past 20 years (Table 7), It is difficult to derive a reasonable estimate of the magnitude or the etiology of this problem of postoperative neuropsychiatric dysfunction. In various reports, the incidence has ranged from 7% to 44% for transient and 1.6% to 23% for persistent sequelae, both more and less than the

TABLE 6

Hemodynamic Variables and Incidence of Postoperative Cerebral Dysfunction*

	No. of patients	Duration of bypass	Patients with blood pressure <50 torr	Of patients with blood pressure <50 torr	
				Duration	Lowest
		min	%	min	torr
Coronary artery bypass operations					
With dysfunction	20	59.1 ± 19.7	60	11.6 ± 7.7	34.5 ± 5.7
Without dysfunction	139	55.7 ± 16.5	73	15.7 ± 11.7	35.6 ± 6.4
Open ventricle operations					
With dysfunction	13	56.8 ± 25.7	46	9.7 ± 6.4	37.5 ± 5.5
Without dysfunction	32	55.2 ± 26.7	59	16.2 ± 13.0	38.4 ± 3.9

* Values are means ± SD.

TABLE 7

Studies Reporting Incidence of Cerebral Dysfunction after Open Heart Operations*

Study	No. of patients	Perspec-tive	Observation	Incidence		Operation	Prime
				Transient	Persistent		
				%			
Ehrenhaft et al (1), 1961	244	R	C	7.0	1.6	I	NR
Gilman (2), 1965	35	P	C & P	34.0	23.0	I	NR
Kornfeld et al (23), 1965	78	P	C & P	38.0	NR	I	NR
Gilberstadt and Sako (24), 1967	53	P	C & P	13.0	13.0	I	NR
Tufo et al (3), 1970	85	P	C & P	44.0	15.0	I	B
Lee et al (25), 1971	71	P	C & P	31.0	NR	I	B
Branthwaite (26), 1972	417	R	C	19.2	9.1	I	B
Stockard et al (8), 1973	25	P	C	36.0	12.1	I & E	NR
Branthwaite (9), 1975	528	R	C	7.4	4.8	I & E	B
Aberg and Kihlgren (4), 1977	223	P	C & P	8.5	NR	I & E	B & C
Ellis et al (10), 1980	30	P	C & P	0	0	E	C
Breuer et al (27), 1980	418	R	C	16.0	NR	E	NR
Kolkka and Hilberman (11), 1980	204	P	C & P	40.0	17.2	I & E	C
Turnipseed et al (12), 1980	170	R	C	NR	5.3	E	C
Present study	204	P	C & P	16.2	6.4	I & E	C

* Abbreviations used are: R, retrospective; P, prospective; C, clinical; P, psychometric; I, intracardiac; E, extracardiac; B, blood; C, crystalloid only; NR, not reported.

findings in the present study (16.2% and 6.4%). A critical review of these published data provided some insights into the reasons for the large variation.

Retrospective versus Prospective Studies

As complications are searched for in prospective studies, a higher incidence can be expected. In the prospective studies listed in Table 7, the incidence of neurologic sequelae was 28.7% among 804 patients contrasted to 11.9% of 1787 patients studied retrospectively. A retrospective chart study of our patients revealed a 2.5% incidence of neurologic sequelae, representing the number considered of sufficient magnitude to warrant recording by attending physicians.

Sensitivity versus Specificity

The criteria used for the presence of a neurologic deficit have varied in published reports from the highly specific but lowly sensitive gross neurologic changes, to highly sensitive but lowly specific psychometric tests. Of patients listed in Table 7, 779 were evaluated by psychometric testing as well as neurologic examination and cerebral dysfunction was considered present in 27.9%. By contrast, 11.3% of 1812 patients were considered neurologically abnormal when only neuropsychiatric and autopsy examinations were included as criteria. In the study by Tufo et al (3), the highest incidence of transient neurologic sequelae was reported but an excessively sensitive nonpsychometric criterion was used. The deficit in 35 of their 37 neurologically abnormal patients consisted only of a positive Babinski reflex. As postoperative neurologic deficits include peripheral neuropathies owing to abnormal body positions, excessive sternal retraction, and intramuscular injections, inclusion criteria must attempt to discriminate peripheral from central deficits. Our study attempted to increase sensitivity by using the Trail Making Test, which is highly specific for organic brain damage, and to increase specificity by requiring two complementary neurologic abnormalities for inclusion of patients in the neurologically abnormal group.

Hypotension, Hypothermia, and Hemodilution

Traditionally, focal neurologic dysfunction occurring after any operation has been ascribed to intraoperative hypotension when no more obvious cause was apparent. When hypotension was profound and prolonged this relationship has been clear. For what period of time lesser degrees of hypotension are

required for neurologic damage is not at all clear, nor do the cumulative data in Table 7 help define this relationship. There is no generally accepted criterion for hypotension and its definition is usually related to some preoperative blood pressure measured under undefined conditions. Hypotension occurring before and after bypass is not usually distinguished from hypotension during bypass despite their widely differing implications. For example, hypotension before or after bypass is usually secondary to blood loss, arrhythmias, or loss of myocardial contractility and is associated with an unknown cardiac output in a normothermic nonheparinized patient. By contrast, cardiac output (perfusion flow rate) is known when hypotension occurs during bypass and hypotension appears when the patient is heparinized and somewhat hypothermic, both of which tend to increase the tolerance of the brain to ischemia. Further, perfusion pressure during cardiopulmonary bypass is related to the composition of the prime and the resulting hematocrit. At identical flow rates, perfusion pressure varies directly with hematocrit because of the effect of hemodilution on whole blood viscosity. Many of these factors have not been separated out or even recorded by previous investigators who suggested hypotension as a precipitating cause of neurologic deficits (2, 3, 8, 9, 25). In the present study, patients with hypotension for greater than 3 minutes from any cause before or after bypass were excluded, limiting hypotension as a factor to that occurring during cardiopulmonary bypass alone. We are unable to identify perfusion pressures of less than 50 torr persisting for 16 minutes associated with hematocrit less than 30% as responsible for neurologic deficits in our patients.

Against this background the study of Stockard et al (8), which implicated hypotension as a cause of postoperative neurologic dysfunction, deserves special comment because of its wide citation. In their study, hypotension was quantified as $T_m - 50$; i.e., 50 torr minus mean blood pressure less than 50 torr multiplied by the minutes it remained less than 50 torr. For example, 40 torr for 10 minutes resulted in a $T_m - 50$ of 100. Twenty-five patients were studied. Hypothermia was used during bypass, but neither the prime nor the hematocrit was reported. Of their first nine patients, seven had $T_m - 50$ values greater than 100 and six of these suffered severe and even fatal neurologic complications. In the next 16 patients vasopressors were administered prophylactically and no neurologic sequelae occurred. In a more recent study by Kolkka and Hilberman (11) $T_m - 50$ values of 500

to 800 were not significantly associated with neurologic deficits. In our study the percentage of patients with mean blood pressure less than 50 torr and the duration of mean blood pressure less than 50 torr were both higher in the groups without cerebral dysfunction (Table 6). Our data, like those of Kolkka and Hilberman (11), fail to support the utility of T_m—50 as an index of cerebral hypoperfusion.

Duration of Perfusion

In several studies (5, 10, 23–25), a statistically valid relationship between duration of perfusion and the incidence of neurologic deficits was found. It is not clear why this should be so, unless duration reflects difficulty of operation and greater likelihood of air or particulate embolization. Possibly microaggregates in the perfusion increase in size with increasing duration of perfusion. Were this so, the use of arterial filters should result in a meaningful reduction in neurologic complications. Such clinical data are not available to support this. Although our data do not support duration of perfusion as a significant predisposing factor, our range of values for duration was not large.

Extracardiac Operations and Emboli

An unequivocal cause of neurologic deficits is air or particulate emboli dislodged from the aorta or cardiac chambers at the time of cannulation or after termination of bypass. The risk of emboli is obviously greater in intracardiac operations (28.9% versus 12.6% in our patients), but is also present in extracardiac operations (CAB) where air or particulate matter can arise from the cannulated ascending aorta and pass to the cerebral vessels. In our patients, more than 75% of whom underwent CAB, nine suffered focal motor or sensory deficit (4/45 intracardiac and 5/159 extracardiac). In eight of these nine patients, the deficit involved the right hemisphere, strongly suggesting an embolus passing up the first great vessel arising from the aorta rather than regional cerebral ischemia as the cause, even in extracardiac operations. Were emboli from these sources the major cause of neurologic deficits, in-line arterial filters would have little impact on this complication.

Age

The development of the CAB operation exposed a much older population to the hazards of cardiopulmonary bypass and enabled the recognition of age as a predisposing factor even in the absence of open

cardiotomy (4, 5, 8, 9). In our data, patients 60 year of age and older suffered 4.5 times the neurologic complications of those less than age 60 years. As patients with known cerebrovascular disease by history or physical examination were excluded from our study, the association between age and neurologic sequelae is not related to clinically evident cerebral vascular insufficiency. Turnipseed et al (12) questioned this relationship between cardiovascular disease and neurologic complications following cardiopulmonary bypass. Among their 170 patients undergoing CAB, 34% had either a cervical bruit or a history of transient cerebral ischemia. Yet the incidence of cerebral complications in this group was only 3.5% (2/57) compared with 6.5% (7/113) in their patients without cerebrovascular disease.

To test the possibility that hypotension and increased age combined is a cause of neurologic dysfunction, we analyzed this relationship and could find no significant interaction. In fact, the subgroup with the least hypotension was the group older than 60 years of age with neurologic abnormalities. In addition, 75% (30/40) of patients 60 years old or older with no postoperative dysfunction had perfusion pressures lower than 50 torr in contrast to only 41% (9/22) of those with dysfunction. Although we have no explanation for the relationship between age and neurologic dysfunction, it should be remembered that with increasing age, cerebral response to extrinsic (environmental) and intrinsic (drugs) stimuli are altered independently of any cerebrovascular disease and that subclinical cerebrovascular disease is probably age related.

Oxygenator Prime

The use of blood for part or all the priming volume of the oxygenator increases the hematocrit as well as the volume of potential particulate matter in the perfusate. The higher hematocrit by increasing viscosity leads to higher intravascular pressures at the same flow from the oxygenator. In this regard it is interesting that most reports that incriminate hypotension as a cause of neurologic dysfunction utilized a blood prime (3, 9, 25). Both Branthwaite (9) and Aberg and Kihlgren (4) reported an appreciable reduction in postoperative neurologic dysfunction among their patients when they converted from a blood prime to an acellular one. Whether the improvement they noted was the result of improved rheologic characteristics of the lower hematocrit perfusate or the decreased volume of particulate matter for embolization could not be determined.

In summary, our review of these reports of neuro-psychiatric dysfunction after open heart operations identified some reasons for the wide variation in the reported incidence. Against this background, we believe our data suggest that embolized air or particulate matter is the major cause of this complication and advancing age is a strong predisposing factor. We were unable to confirm a perfusion pressure of less than 50 torr as either predisposing or causative.

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Functional and Structural Changes in the Rabbit Vagus Nerve in Vivo following Exposure to Various Hypoosmotic Solutions

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BARSA, J., FINK, B. R., SUMI, S. M., AND CALKINS, D. F.: Functional and structural changes in the rabbit vagus nerve in vivo following exposure to various hypoosmotic solutions. Anesth Analg 1982;61:912–6.

Hypoosmolar solutions were recently shown to produce a reversible conduction block of rabbit vagus nerve and to potentiate local anesthetic agents. The object of the present study was to determine the ability of neural tissue to recover structurally and functionally following exposure to hypoosmotic solutions. Cervical vagus nerves of rabbits were bathed in situ for 2 hours in a control solution or in 0.4, 0.5, and 0.6 aqueous dilutions of physiologic salt solution. Nerves excised immediately after exposure, or 1 or 4 weeks later, were subjected to light and electron microscopic examination. Following exposure to control and 0.6 dilution, nerves were normal in all respects at 8 days. However, nerves exposed to 0.4 and 0.5 dilutions, although apparently functionally intact as tested by conduction of C fiber action potentials, showed evidence of axonal damage characterized by accumulation of macrophages and proliferation of Schwann cell processes. It may be inferred that the osmotic fragility of axons is similar to that of erythrocytes and that immersion in 0.6 N osmotic solution is probably harmless to the nerve.

Key Words: TOXICITY: neurotoxicity, hypoosmotic; NERVE: hypoosmotic solutions.

H YPOOSMOLAR solutions were recently shown to produce a reversible impairment of nerve impulse conduction and to potentiate the in vitro blocking action of the local anesthetic lidocaine (1–3). Clinically, these effects of hypoosmolarity may be of importance when hypobaric spinal anesthesia is used as hypobaric spinal anesthetic solutions are also hypoosmolar (4). Hypobaric spinal anesthetic solutions are made up by dissolving a local anesthetic in water (5–7), and are often injected in a large volume that produces an initial hypoosmolar dilution of the cerebrospinal fluid (4). Extreme hypoosmotic dilution of cerebrospinal fluid has been used to obtain partial pain relief by selective destruction of C fibers in patients with advanced metastatic cancer (8, 9).

The object of the present study was to determine the ability of neural tissue to recover structurally as well as functionally following exposure to graded hypoosmolarity.

Methods

The experiments were performed on the cervical portion of the vagus nerve in rabbits. Following induction of anesthesia with halothane and oxygen, the rabbit was restrained in the supine position. After the skin was shaved from the mandible to the upper sternum and painted with alcohol and tincture of iodine, a 10- to 12-cm incision was made in the midline. The superficial fascia was exposed by blunt dissection and incised on both sides approximately 0.5 cm lateral to the trachea. The sternohyoid and the sternomastoid muscles were separated by blunt dissection on both sides of the trachea and retracted by nylon traction sutures attached to an overlying ring support, thereby forming a unilateral or bilateral trough which could be filled with test or control solutions. The cervical vagus nerve was visible lying within the carotid sheath at the bottom of the trough.

The sheath was then incised and the vagus nerve was gently separated from the carotid artery. Oxygenated solution at 38°C was introduced into the trough and replenished as required so as to ensure continuous immersion of the nerve for 2 hours. A heating lamp and blanket maintained the temperature of the rabbit at 38 to 39°C. Samples (0.2 ml) of trough fluid were removed every 15 minutes for measurement of sodium and potassium concentrations. In some animals the vagus nerves were removed immediately after exposure. In others the skin was closed with metal clips, and the animal was allowed to recover. These animals were killed by air embolism 1 to 4 weeks later, and the vagus nerves removed for examination.

The control solution consisted of physiologic isotonic salt solution (Gibco M199, catalog number 400-1100, Grand Island Biological Company, Long Island, NY). Test solutions consisted of the same solution diluted with water to 0.6, 0.5, or 0.4 of control osmolarity, as tested in a Wescor osmometer.

A total of 22 vagus nerves were studied (11 animals). The schedule of treatment to which these animals have been subjected was as follows:

Group 1: Controls

In animals 1 to 3, the right vagus nerves were exposed to air for 15 minutes but no solution was added. The left vagus nerves were not exposed. These control nerves were used to test the possible effects of anesthesia, surgery, and exposure of the nerve to air alone. In animals 4 to 11, the right vagus nerves were exposed to physiologic solution for 2 hours.

Groups 2 to 4

Group 2 included animals 4, 6, and 7. In these rabbits, the left nerves were exposed to 0.6 hypoosmotic solution for 2 hours. Group 3 included animals 5, 8, 9, and 10. In these rabbits, the left nerves were exposed to 0.5 hypoosmotic solution for 2 hours. Group 4 consisted of animal 11. In this rabbit, the left nerve was exposed to 0.4 hypoosmotic solution for 2 hours.

Animals 1, 4, and 5 were killed and the nerves processed at the end of the exposure period. The remaining animals in all the groups were killed and the nerves examined 8 or 28 days later (Table 1). After excision, all nerves were placed in Ringer's solution. Conduction in C fibers was tested by placing the nerve on an array of platinum wire stimulating and recording electrodes, and applying a supramaximal 75-V, 0.1-msec stimulus from a Grass S44 stimulator and stimulus isolation unit. The compound action potential was displayed on a Tektronix 532 cathode ray oscilloscope and photographed with a Polaroid camera.

Tissue specimens were collected from the proximal, middle, and distal parts of each nerve, fixed in 0.25% glutaraldehyde + 4% paraformaldehyde in 0.13 M sodium phosphate (pH 7.2) postfixed in buffered osmium tetroxide, and embedded in Epon; nine to 11 sections, 0.5- to 2-μ thick, from each nerve, were stained with methylene blue or azur blue II for light microscopy. Thin sections from the same blocks were stained with uranyl acetate and lead citrate for electron microscopy. Microscopic examinations were per-

TABLE 1

Effect of Hypoosmotic Solutions on Gross Appearance and Conduction of Nerves

Treatment group	Animal no.	No. of nerves	Duration of treatment	Time interval to examination	Action potential*	Gross appearance
			min	*days*		
1 (control nerves)						
A. None	1	2	—	0	+	Normal
	2	2	—	8	+	Normal
	3	2	—	28	+	Normal
B. Physiologic solution	4, 5	2	120	0	+	Normal
	6–9	4	120	8	+	Normal
	10, 11	2	120	28	+	Normal
2 (0.6 hypoosmotic)	4	1	120	0	+	Normal
	7	1	120	8	+	Normal
	6	1	120	28	+	Normal
3 (0.5 hypoosmotic)	5	1	120	0	+	Mild nerve swelling
	8, 9	2	120	8	+	Mild adhesion and nerve swelling
	10	1	120	28	+	Mild adhesion and nerve swelling
4 (0.4 hypoosmotic)	11	1	120	8	+	Moderate adhesion and nerve swelling

* Symbol used is: +, normal C-fiber potential.

formed by S.M.S., who was unaware of the treatment to which the nerves had been subjected.

Results

The gross appearances of the nerves and the results of the conduction tests are summarized in Table 1. Unexposed nerves and those exposed to air only (group 1A), to physiologic control solution (group 1B), and to 0.6 hypoosmotic solution (group 2) were grossly normal in all respects. Nerves exposed to 0.5 hypoosmotic solution (group 3) and to 0.4 hypoosmotic solution (group 4) were swollen and were adherent to surrounding tissue when examined at 8 days. However, these nerves were normal when tested for conduction (Table 1).

Light and electron microscopic examination revealed no abnormality in either nerves exposed to 0.6 hypoosmotic solution (group 2) or in control nerves (group 1). At 8 days light microscopy showed that most of the axons, both myelinated and unmyelinated, appeared to be well preserved in nerves exposed to 0.5 and 0.4 hypoosmotic solution (groups 3 and 4). However, several round lipid-filled macrophages were present in these nerves. Electron microscopic examination revealed clusters of proliferating Schwann cell processes (bands of Büngner), as well as the presence of both macrophages and Schwann cells containing lipid droplets and myelin fragments (Figs 1 to 3).

Sodium and potassium concentrations in the solutions taken from the trough during the exposures are summarized in Table 2. There was relatively little change in their concentrations during the period of exposure.

Discussion

The osmotic strengths 0.6 and 0.5 (physiologic osmolarity = 1.0) were selected for testing because these strengths are, respectively, smaller and greater than those critical for hemolysis of red cells (10). Occasional Schwann cell infiltration by macrophages together with bands of Büngner with lipid inclusions were observed in some specimens obtained 8 days after exposure to 0.5 hypoosmotic solution. No ultrastructural abnormalities could be seen following exposure to 0.6 hypoosmotic solution (Figs 1 to 3). However, in nerves exposed to 0.4 and 0.5 hypoosmotic solutions most of the axons, both myelinated and unmyelinated, had no detectable ultrastructural defects. This explains the functional integrity in these nerves as tested by conduction of C fiber action potentials.

The ability of neural tissue to recover structurally, as well as functionally, from exposure to hypoosmotic solution is probably determined by the duration of exposure and the magnitude of hypoosmolarity. In the present study, the hypoosmotic exposure was severe and maintained for 2 hours as evidenced by the concentration of sodium and potassium in the trough solution sampled throughout the period of exposure.
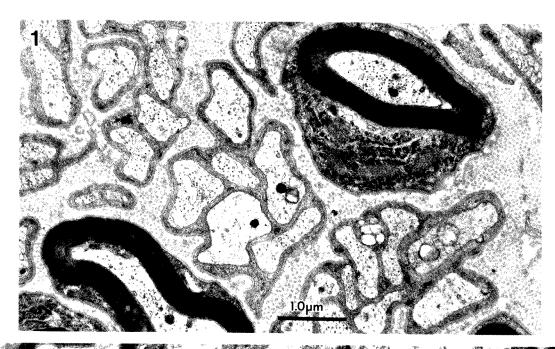
In a study of 1640 cases of hypobaric tetracaine spinal anesthesia, Lund and Rumball (6) reported no neurologic complications. They prepared their spinal anesthetic solutions by dissolving tetracaine crystals in pure water. The volume of intrathecal injection was 5 to 20 ml and the concentration of tetracaine varied between 0.05% to 0.1%, which in the Wescor osmometer yields an osmolarity of 2 to 20 mOsmol/L. We
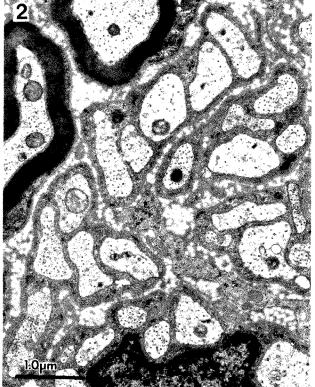
TABLE 2

Sodium (Na) and Potassium (K) Concentrations in Trough Solutions at 15-Minute Intervals*
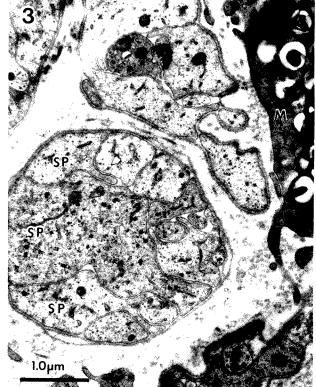
Observation time	Solution osmolarity†							
	0.4		0.5		0.6		1	
	Na	K	Na	K	Na	K	Na	K
min				*meq/L*				
15	57 ± 4	2.2 ± 0.1	76 ± 3	2.8 ± 0.2	93 ± 9	3.2 ± 0.2	130 ± 2	4.9 ± 0.2
30	60 ± 3	2.1 ± 0.3	75 ± 4	2.8 ± 0.1	96 ± 3	3.3 ± 0.3	139 ± 4	5.0 ± 0.1
45	56 ± 6	2.1 ± 0.1	73 ± 6	2.7 ± 0.2	89 ± 5	3.0 ± 0.1	134 ± 2	4.8 ± 0.3
60	62 ± 2	2.4 ± 0.1	86 ± 9	3.1 ± 0.3	93 ± 2	3.2 ± 0.1	139 ± 1	5.2 ± 0.2
75	56 ± 7	2.3 ± 0.2	81 ± 3	3.1 ± 0.2	97 ± 6	3.3 ± 0.2	142 ± 4	5.2 ± 0.2
90	59 ± 3	2.1 ± 0.1	73 ± 5	2.8 ± 0.1	93 ± 7	3.2 ± 0.3	137 ± 3	4.4 ± 0.3
105					88 ± 2	3.2 ± 0.3	141 ± 2	5.0 ± 0.3
120					93 ± 6	3.2 ± 0.1		

* Values are means ± SE.
† Physiological osmolarity = 1.0.

FIGS 1 TO 3. Electron micrographs of nerves excised 8 days after exposure. Fig 1, Control; Fig 2, 0.6 hypoosmotic solution; Fig. 3, 0.5 hypoosmotic solution. In Figs 1 and 2 both myelinated and unmyelinated fibers are well preserved. In Fig 3 there are proliferating Schwann cell processes (SP) bound by a basement membrane (band of Büngner), and a portion of a macrophage (M) containing lipid droplets and myelin fragments.

have found (unpublished data) that the osmolarity of cerebrospinal fluid obtained 5 to 10 minutes following the intrathecal injection of hypoosmotic tetracaine solution similar to that used by Lund and Rumball is approximately 0.6 of N.

Our present observations suggested that the os-

motic fragility of axons is similar to that of red blood cells (10). Negative results observed with the 0.6 dilution do not necessarily imply that the same dilution containing local anesthetic would be equally inert if used in peripheral nerve blocks or in the epidural region.

The results reported here suggest that, within limits, hypoosmolarity as such presents little or no long-term hazard to nerve.

ACKNOWLEDGMENT

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Dobutamine and Cardiac Oxygen Balance in Patients following Myocardial Revascularization

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Dobutamine is frequently used in the early postoperative period following myocardial revascularization to improve cardiac output. Seven postoperative adult patients with low output syndrome were studied before and during intravenous dobutamine (mean ± SD: 5.1 ± 2.5 µg/kg/min) infusion. The metabolic effects were evaluated and related to hemodynamic changes. Cardiac index increased 40% ($p < 0.05$) with an increase in heart rate ($p < 0.05$) and decreases in systemic vascular resistance and right atrial pressure ($p < 0.05$). No significant changes occurred in arterial or pulmonary capillary wedge pressures or in stroke volume index. Dobutamine produced a 29% increase in myocardial oxygen consumption which, in these revascularized patients, was accompanied by a 35% increase in coronary blood flow. No significant alteration was observed in coronary sinus oxygen content or in global myocardial lactate extraction. Thus, despite the increased metabolic cost of dobutamine, global myocardial ischemia was not observed.

Key Words: HEART: dobutamine; SYMPATHETIC NERVOUS SYSTEM: dobutamine; SURGERY: cardiovascular; ANESTHESIA: cardiovascular.

D OBUTAMINE, a synthetic catecholamine and a potent beta-1 receptor agonist, improves left ventricular function by its positive inotropic effect (1–3). Recently, studies of the systemic hemodynamic effects of dobutamine in patients following open-heart surgery have shown improved left ventricular function with increases in heart rate, mean arterial pressure, cardiac index, and stroke volume index (4, 5). Any consideration of the benefit must be made in

relation to the effects of the drug on myocardial oxygen supply and demand, as dobutamine may constitute an undesirable metabolic cost to the myocardium simultaneous with its salutary clinical effect (6). An evaluation of the metabolic costs of dobutamine administered for management of postoperative low cardiac output following myocardial revascularization has not been described. Accordingly, the goal of this study was to examine the acute effects of dobutamine on myocardial oxygen consumption and myocardial lactate extraction in patients following coronary artery bypass surgery, relating the data to concurrent changes in hemodynamics.

Methods and Materials

According to a protocol approved by the Human Subjects Committee, seven consecutive patients (five men, two women; mean age 48 years) were studied. All patients had low cardiac output syndromes before dobutamine administration; the cardiac index was low, whereas heart rate and pulmonary capillary wedge pressure were within normal limits. Informed consent was obtained from all patients. The study was done in the cardiac surgical intensive care unit within

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the first 6 hours following myocardial revascularization. All patients were sedated and were being mechanically ventilated. One patient received morphine sulfate, 3 mg, and diazepam, 5 mg, intravenously 20 minuted before dobutamine infusion; another patient received morphine sulfate, 4 mg, and diazepam, 5 mg, intravenously 50 minutes before dobutamine infusion. None of the remaining patients received a vasoactive drug whose effect might have persisted at the time of the study.

Before surgery, all patients had chronic stable angina or medically controlled unstable angina. Mean preoperative angiographic ejection fraction was normal (0.77 ± 0.07, mean ± SD). One patient had single-vessel disease, four patients had double-vessel disease, and two patients had triple-vessel coronary disease. Five patients had been anesthetized with morphine sulfate (1 mg/kg IV) and two patients with halothane-oxygen. In the latter two patients, induction of anesthesia with halothane began with up to 2.5% halothane inspired in oxygen, and thereafter anesthesia was maintained with 0.5% to 0.1% halothane in oxygen. The vein grafts were performed during whole body perfusion with core cooling at 20 to 25°C. Crystalloid potassium or blood cardioplegia and topical myocardial hypothermia (4°C) were utilized. The mean ischemic time on cardiopulmonary bypass was 77 ± 29 minutes. Diseased coronary arteries in each patient were judged to be completely revascularized by the surgeon (number of grafts, range: 2 to 5), as all vessels with greater than 50% obstruction were bypassed. No patient developed perioperative myocardial infarction by serial electrocardiographic or enzymatic alterations.

The following catheters had been introduced before surgery in each patient: (a) an 18-gauge cannula in the radial artery; (b) a thermodilution triple-lumen catheter (Edwards, Santa Ana, CA) by the Seldinger technique through the right internal jugular vein into the pulmonary artery; and (c) a coronary sinus catheter (Wilton-Webster Laboratories, Altadena, CA) through the same internal jugular vein into the coronary sinus by fluoroscopy, so that the external thermistor was 10 to 20 mm inside the coronary sinus.

After control measurements, dobutamine (mean dose, 5.1 ± 2.5 µg/kg/min) was infused intravenously over an average period of 26 minutes. The drug was titrated to increase cardiac index by at least 25% without development of adverse effects. Coronary sinus blood flow was measured by the thermodilution technique described by Ganz et al (7). Arterial and coronary sinus blood samples were obtained simul-

taneously for determinations of lactate and oxygen concentration. Lactate samples were analyzed in duplicate by a modification of the Marbach method (8). Blood samples were analyzed immediately for oxygen saturation and hemoglobin concentration (IL Co-Oximeter model 282). Oxygen content (milliliters per deciliter) was calculated as: hemoglobin $\times$ O_2% saturation $\times$ 1.34. Systemic and pulmonary arterial, pulmonary capillary wedge, and right atrial pressures were recorded and measured on paper using a six-channel chart recorder (VR-6 Electronics for Medicine). Cardiac output was measured in duplicate by thermodilution. Arterial blood pressure, electrocardiogram, and the patient's clinical condition were continually monitored. All measurements were repeated after the dobutamine infusion.

Hemodynamic indices were calculated from pressure and cardiac output data according to standard formulas. Metabolic indices were calculated as follows:

$$\text{lactate extraction ratio} = \frac{\text{ART (lactate)} - \text{CS (lactate)}}{\text{ART (lactate)}}$$

where ART (lactate) is the arterial lactate concentration (milliequivalents per liter) and CS (lactate) is the coronary sinus lactate concentration (milliequivalents per liter).

$$MV_{O_2} = CBF \times (ART \{oxygen\} - CS \{oxygen\})$$

where MV_{O_2} is oxygen consumption of the myocardium drained by the coronoary sinus (predominantly the left ventricular myocardium) and CBF is coronary sinus blood flow.

Statistical evaluation was performed using a paired t-test comparing measurements before and after dobutamine administration in each patient. Results are expressed as means ± standard deviation. A "p" value of less than 0.05 was considered statistically significant.

Results

Hemodynamic data before and after the dobutamine infusion are summarized in Table 1. The patients had low cardiac output syndromes before dobutamine administration; the cardiac index was low (1.64 ± 0.4 L/min/m^2), whereas heart rate and pulmonary capillary wedge pressure were within normal limits. Following dobutamine infusion, the cardiac index increased 40% ($p < 0.05$), a response due predominantly to an increased heart rate as stroke volume index was not significantly changed. This was accompanied by significant reductions in systemic

TABLE 1

Hemodynamic Response to Dobutamine In Patients (N = 7) following Coronary Artery Bypass Surgery*

Intervention	HR	MAP	PCWP	RA	SVR	CI	SVI
	beats/min		*mm Hg*		*dynes·sec·cm⁻⁵*	*L/min/m²*	*ml/beat/m²*
Before	70 ± 7	85 ± 12	12 ± 2	10 ± 3	2141 ± 806	1.64 ± 0.37	23 ± 5
After	87 ± 4	90 ± 14	10 ± 4	7 ± 3	1708 ± 642	2.29 ± 0.60	26 ± 7
Significance	$p < 0.05$	NS	NS	$p < 0.05$	$p < 0.05$	$p < 0.05$	NS

* Values are means ± SD. Abbreviations used are: HR, heart rate; MAP, systemic mean arterial pressure; PCWP, mean pulmonary capillary wedge pressure; RA, mean right atrial pressure; SVR, systemic vascular resistance; CI, cardiac index; SVI, stroke volume index; NS, not significant.

vascular resistance and right atrial pressure. Although left ventricular stroke work index increased 36% (30.0 ± 8 to 40.9 ± 16 g·m/m²), this change was not statistically significant.

Myocardial metabolic data are shown in Table 2. Dobutamine produced an increase in the calculated myocardial oxygen consumption in six patients with a mean increase of 29% for the entire group ($p < 0.05$). This was accompanied by a parallel increase in coronary blood flow in the same patients resulting in an overall 35% increase for the group ($p < 0.05$). The mean coronary sinus oxygen content for the group remained unchanged. Alterations in the mean global myocardial lactate extraction for the entire group were not statistically significant. One patient had a slight reduction in myocardial oxygen consumption and coronary blood flow with an increase in coronary sinus oxygen content.

The two patients who received morphine sulfate within 1 hour of the study did not show a different response to dobutamine compared with the remaining five patients.

None of the patients experienced an adverse reaction during the study. Continued electrocardiographic monitoring showed no alterations in cardiac rhythm, ST segments, or T waves.

Discussion

Although dobutamine is frequently used for management of low cardiac output following myocardial revascularization (4, 5), the myocardial metabolic cost imposed by the drug in this setting is unknown. Our study examined the myocardial metabolic cost of dobutamine, specifically its effects on myocardial oxygen supply and demand.

It is important to describe in detail the patients studied, because the results obtained in one clinical or hemodynamic setting may not apply to all patients. Each patient was judged to be completely revascularized by the surgeon. The study was performed within 6 hours of the surgery, and the patients had a low

TABLE 2

Myocardial Metabolic Response to Dobutamine In Patients (N = 7) following Coronary Artery Bypass Surgery*

Intervention	CBF	CS-O₂ content	MVo₂	MLE
	ml/min	*ml/dl*	*ml/min*	%
Before	101 ± 45	6.1 ± 1.0	8.2 ± 3.3	16 ± 14
After	136 ± 59	6.3 ± 1.1	10.6 ± 4.0	21 ± 17
Significance	$p < 0.05$	NS	$p < 0.05$	NS

* Values are means ± SD. Abbreviations used are: CBF, coronary sinus blood flow; CS-O₂, oxygen content in coronary sinus blood; MVo₂, myocardial oxygen consumption; MLE, myocardial lactate extraction.

cardiac index with heart rate and pulmonary capillary wedge pressure within normal limits.

This study confirms the beneficial hemodynamic effects of dobutamine in patients with postoperative low cardiac index, as the cardiac index increased in all patients whereas right atrial pressure decreased and pulmonary capillary wedge pressure did not change. Contrary to results previously reported by us and other investigators (4, 5), the improvement in cardiac index in our patients was due largely to an increase in heart rate rather than to improvement in stroke volume index. Although the stroke volume index increased by 13%, the increase was not statistically significant. Differences in findings in patients in this study and the patients previously described by our group relates to the techniques of surgery and the time following surgery at which the study was performed. The present patients were studied 2 to 6 hours after surgery in which cardioplegia was used, and they were studied when they were still cold (mean body temperature = 35°C); whereas the patients previously reported by us were operated on using intermittent aortic cross-clamping with moderate hypothermia (28°C) without cardioplegia, and the patients had been warmed to normal body temperature at the time of the study (5). Thus, whatever adverse influence hypothermia and cardioplegia may have on myocardial performance in the first few hours following

surgery may have been expressed in the present study. Although it is conceivable that the observed reduction in systemic vascular resistance may have contributed to the left ventricular function in our patients, experimental studies suggest that at the doses used in this study, dobutamine exerts little or no direct effect on arteriolar tone, and therefore the reduction of systemic vascular resistance is likely to be secondary and reflex in origin.

There was a significant increase in myocardial oxygen consumption associated with improved left ventricular function in our patients. Increased myocardial oxygen consumption was almost solely due to increased coronary blood flow because myocardial oxygen extraction remained unchanged. An increased oxygen demand secondary to tachycardia is the most likely explanation for the increased oxygen consumption; there was a tendency toward a higher rate-pressure product in our patients during dobutamine infusion. Despite a significant increase in myocardial oxygen consumption, deterioration in myocardial metabolic function was not observed as transmyocardial lactate extraction remained unchanged. These findings suggest that increased myocardial oxygen consumption associated with the use of chronotropic agents following myocardial revascularization does not necessarily produce deleterious myocardial ischemia as manifest by adverse metabolic effects.

Limitations of the technique for measuring coronary sinus blood flow used in this study have been summarized elsewhere (9, 10). We feel this technique provides meaningful information regarding the magnitude and direction of changes in coronary blood flow when measured sequentially in the same patient. A potential technical criticism relates to the validity of comparative coronary sinus blood flow determinations by the thermodilution technique when right atrial pressure is elevated (11). In all patients, the positional stability of the catheter in the coronary sinus and the absence of major reflux into the mouth of the coronary sinus was assessed as suggested by Mathey et al (11). Furthermore, there was a decrease in right atrial pressure with dobutamine, which should decrease coronary sinus reflux.

Some caution should be introduced concerning the myocardial safety of dobutamine in all patients following myocardial revascularization as derived from our data. Alterations in regional myocardial blood flow and regional myocardial metabolism may not be reflected in the overall global evaluation of myocardial metabolic function. Our study could not examine regional myocardial pathophysiology, and the regional effects of dobutamine in this setting remain to be determined.

In conclusion, dobutamine in moderate doses improves cardiac output in patients experiencing a low output syndrome following myocardial revascularization. Under the conditions of the present study, this increase in cardiac index is on the basis of an increase in heart rate. Improved left ventricular function is usually associated with increased myocardial oxygen consumption; however, despite this increased metabolic cost, global myocardial ischemia is not observed.

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Criteria for Selection of Ambulatory Surgical Patients and Guidelines for Anesthetic Management: A Retrospective Study of 1553 Cases

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The charts of 1553 patients who were anesthetized for ambulatory surgery were analyzed retrospectively to determine the effect of the type of surgery, the age of the patient, the use of premedication, the duration of anesthesia, and the anesthetic technique on the duration of recovery and the rate of complications. In a 4-month period in 1979, 1073 patients were treated, and another 480 patients were treated during a 2-month period in 1980. Aside from patients undergoing dental surgery, the surgical procedure and the extremes of age affected neither the duration of recovery (193 ± 97 minutes) nor the rate of complications (2.45%). The use of premedicants other than narcotics did not prolong recovery. There was no relationship between anesthesia time and the duration of recovery. Patients who received local anesthesia had a significantly shorter recovery period than the whole population, and significantly fewer patients receiving local anesthesia had to be admitted to the hospital. Thus, arbitrary limits placed on the type of surgery, age of the patient, the duration of the procedure, and the use of certain premedication appear to be unwarranted.

Key Words: ANESTHESIA: outpatient.

IN RECENT YEARS, there has been a proliferation of hospital-based and free-standing ambulatory surgical centers throughout the United States. Day care surgery in a hospital-based setting has been practiced at Hartford Hospital since the 1950s, with 22,031 ambulatory surgical patients having been cared for between October 1975 and October 1981, representing approximately 20% of all surgical cases.

This increase in the number of patients has raised serious questions about the criteria for selection of suitable candidates for ambulatory surgery and guidelines for their anesthetic management. Type of surgery, age, use of premedication, duration of anesthesia, and anesthetic technique have all been proposed as criteria for patient selection and guidelines for anesthetic care (1–6). Nevertheless, it has not been possible to define precisely the factors that contribute to a successful outcome of ambulatory surgery.

This retrospective study reviews 1553 patients who underwent surgery and anesthesia at Hartford Hos-

pital in the One-Day Surgery Unit, which opened as a self-contained unit in 1979. The purpose of this review is to determine what effects—if any—age, use of premedication, duration of anesthesia, and anesthetic technique may have had on the outcome, i.e., the duration of the recovery as well as the rate and nature of complications incurred. To assess the value of 1 year of experience in operating the newly established, self-contained unit, two time spans, 1 year apart, were selected.

Methods

Two sets of data were compiled: (a) records of 1073 patients treated from September through December 1979, and (b) records of 480 patients treated in September and October 1980. Surgical procedure, age, sex, premedication, anesthetic agent, and technique were recorded. Duration of anesthesia, determined as the time spent in the operative suite, and recovery time, defined as the amount of time between leaving the operative suite and discharge from the unit, were recorded. All data were coded and processed with an IBM 34 series computer, where they were stored, sorted, and analyzed. Statistical analysis included linear regression to determine correlation, the unpaired

Student's t-test to compare mean values, and the chi-square test to determine significant differences in frequency.

The first set of 1073 patients consisted of 802 females and 271 males with ages ranging from 4 to 92 years, mean age of 37 years. The second set of 480 patients included 317 females and 163 males with ages ranging from 9 months to 87 years, mean age of 37 years (Fig 1). All patients were A.S.A. physical status I or II.

Results

The surgical procedures performed were grouped into seven categories: general (16.2%), ophthalmologic (3.4%), urologic (7.6%), gynecologic (34.2%), otolaryngologic (9%), dental (15%), and orthopaedic (14.6%). The relation between the surgical procedure and the length of the anesthesia time can be seen in Table 1. Ophthalmologic procedures approached the mean anesthesia time for the entire population. General and dental surgical, otolaryngologic, and orthopaedic procedures were significantly longer, whereas gynecologic and urologic procedures were significantly shorter. The mean anesthesia time for 1073 patients anesthetized in 1979 was 46 ± 23 minutes with a range of 2 to 170 minutes. For the second series of 480 patients anesthetized in 1980, the mean anesthesia time was 45 ± 24 minutes with a range of 2 to 215 minutes.

Recovery time is used as one of the measures of outcome in this study. The mean recovery time for the patients in the first set was 193 ± 97 minutes in contrast to the significantly shorter mean recovery

time of the second set which was 164 ± 86 minutes ($p < 0.001$). The relation between the surgical procedure and the mean recovery time can be seen in Table 1. Recovery time for gynecologic and otolaryngologic patients did not differ from that of the entire population. Patients recovering from dental surgery had a significantly longer recovery period. The recovery period of 40% of these patients was greater than 294 minutes. Patients recovering from general surgical, orthopaedic, urologic, and ophthalmologic procedures had a significantly shorter recovery period. The recovery period of 52% of these patients was less than 143 minutes.

The data in Table 1 indicate that there is no striking relationship between anesthesia time and recovery time. Orthopaedic procedures, which required the longest anesthesia time, resulted in a recovery time of 155 minutes, which was less than the mean of all cases studied. Furthermore, as anesthesia time is increased, there is no increase in the duration of recovery, as shown in Fig 2.

The relation between the anesthetic techniques and surgical procedures is seen in Fig 3. Analysis of the anesthetic agents administered revealed that 76% of the patients received general anesthesia preceded, in almost all cases, by a thiopental induction. General anesthesia agents administered were: nitrous oxide/oxygen 11%, halothane/nitrous oxide/oxygen 22%, enflurane/nitrous oxide/oxygen 42%, and narcotic/nitrous oxide/oxygen 25%. Halothane/nitrous oxide/oxygen was the most frequently selected anesthetic in the younger age group. In the older age group, local anesthesia was most frequently selected, whereas in
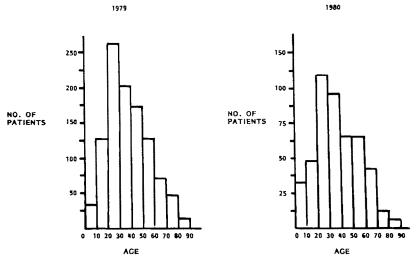
FIG 1. Age distribution.

the middle age group, there was an even distribution of anesthetic agents used.

The relation between anesthetic techniques and the duration of recovery (Table 2) reveals that those patients who received enflurane had a significantly longer recovery period than the population as a whole. Twenty-five percent of patients receiving enflurane anesthesia had a recovery period greater than 294 minutes. Patients who received local anesthesia (i.e., field block or intravenous regional block) had a significantly shorter recovery period. Sixty percent of patients receiving local anesthesia had a recovery period less than 143 minutes.

The number of patients transferred from a day care

TABLE 1

Relationship between Surgical Procedure and Anesthesia and Recovery Times

Procedure	No.	Time*	
		Anesthesia	Recovery
		min	
Dental surgical	180	57 ± 18†	274 ± 78‡
General surgical	193	52 ± 25†	168 ± 87‡
Gynecologic	382	34 ± 15†	203 ± 90
Ophthalmologic	41	49 ± 19	122 ± 89‡
Orthopaedic	109	61 ± 31†	155 ± 85‡
Otolaryngologic	91	57 ± 21†	178 ± 102
Urologic	77	31 ± 14†	126 ± 76‡
All procedures	1073	46 ± 23	193 ± 97

* Values are means ± SD.
† Differed significantly ($p < 0.005$) from mean (46 ± 23).
‡ Differed significantly ($p < 0.001$) from mean (193 ± 97).

FIG 3. Relationship between anesthetic technique and surgical procedures.
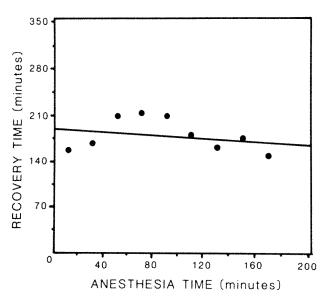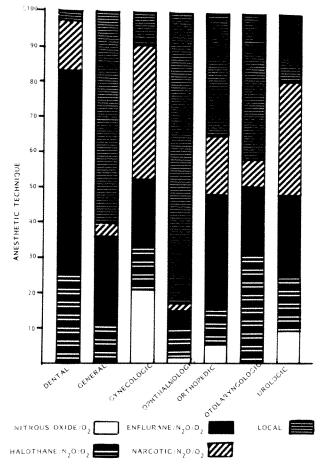
FIG 2. Effect of anesthesia time on recovery time. Slope = −0.1092; intercept = 190.5; $r = -0.2360$.

TABLE 2

Relationship between Anesthetic Agents and Recovery Time

Anesthetic agents	No.	Time*	
		Anesthesia	Recovery
		min	
N_2O/O_2	97	30 ± 10	185 ± 85
Halothane/N_2O/O_2	170	50 ± 21	206 ± 100
Enflurane/N_2O/O_2	301	56 ± 22	236 ± 88†
Narcotic/N_2O/O_2	231	38 ± 19	202 ± 93
Local	274	43 ± 25	136 ± 86‡
All agents	1073	46 ± 23	193 ± 97

* Values are means ± SD.
† Significantly longer than mean ($p < 0.001$).
‡ Significantly shorter than mean ($p < 0.001$).

unit to an inpatient setting can serve as an index of outcome. The percentage of 1553 patients treated at our one-day surgery unit who were transferred to the hospital was 2.44%. It is demonstrated in Table 3 that of the 38 transfers, 0.64% were judged secondary to

anesthesia and 1.8% for surgical reasons. Eighty-seven percent of the patients transferred to the hospital received some form of general anesthesia whereas 13% received local anesthesia.

Of those patients admitted to the hospital because of anesthetic complications, all received general anesthesia. Even though 76% of the patients studied received general anesthesia, the number of complications in this group is larger than would be expected by random chance according to chi-square test ($p <$ 0.05). Although the mean anesthesia time (63 ± 30 minutes) for those patients who were admitted was significantly longer than the mean anesthesia time for the entire population, 71% of these patients had an anesthetic that lasted less than 60 minutes.

The age of the patient might influence the duration of anesthesia, recovery, and the incidence of complications. In Fig 4 is shown that the duration of anesthesia varied little with age. However, the duration of recovery was influenced by age. The younger age

groups had longer recovery times with the longest times associated with the 10- to 19-year-old group. Twenty-seven percent of the 10- to 19-year-old group had a recovery period greater than 294 minutes. On the other hand, it was the 20- to 49-year-old group that comprised 70% of the patients who were transferred to an inhospital setting.

Premedication received by 1553 ambulatory surgical patients is listed in Table 4. Approximately 25% of the patients received a hypnotic and/or narcotic and 40% received atropine. The effect of the use of premedication on the duration of recovery time is measured by comparing the mean recovery time of those patients who received a premedicant with those who did not. The data from this comparison (Table 4) show that premedication had a marginal effect on recovery times, with patients given narcotics having significantly longer recovery times than unmedicated patients.

Discussion

The criteria for the selection of a patient for ambulatory surgery and the guidelines for anesthetic management are normally based on the type of surgery, age of the patient, need for premedication, length of anesthesia, and/or technique (1-6). The question raised by this study is whether or not the surgical or anesthetic stress will alter the patient's physiologic status to such a degree that he will be unable to return home the same day following his anesthetic and surgical experience. From the data presented here and from other studies of one-day surgical patients (1, 2, 6-8), there is a basis to evaluate the criteria that are currently in use.

Type of Surgery

All types of surgical procedures on patients of

TABLE 3

Types of Complications Resulting in Hospital Transfer

Anesthesia related	No. of patients	Surgery related	No. of patients
Nausea and vomiting	8	Pain	9
Epistaxis	1	Bleeding	4
Atrial flutter	1	Temperature	3
		Observation	2
		Surgical misadventure	3
		Errors in diagnosis	7

FIG 4. Relationships between age and anesthesia time and age and recovery time.

TABLE 4

Relationship between Premedication Received by 1553 Patients and Recovery Time

Type	No.	Recovery time*
		min
No premedication	1015	179 ± 113
Diazepam	98	168 ± 104
Pentobarbital	25	231 ± 88
Narcotics (meperidine and morphine)	388	208 ± 101†
Hydroxyzine	92	192 ± 120

* Values are means ± SD.

† Differs significantly from patients not receiving any premedication ($p <$ 0.001).

A.S.A. physical status I or II were accepted by our unit as long as the surgeon was confident that his patient would be physically and mentally able to return home the same day. Except for dental surgical procedures, there was no association between the type and duration of surgery and the outcome, as determined by prolonged recovery and the rate of overnight hospital admission. It is recognized that a high morbidity follows dental surgery (7, 9–11) even if only local analgesia is used. The duration of recovery could be prolonged because these procedures are associated with considerable pain, bleeding, nausea, and vomiting, and may have required the use of postoperative narcotics and antiemetics.

Age of Patient

Our data confirm the finding that the extremes of age are not a deterrent in the selection of ambulatory surgical patients (4, 5). Nevertheless, we found that certain age groups have less favorable ambulatory surgical experiences.

Although it is not unusual that the younger age group was managed primarily with halothane and the older age group with local anesthesia, it was surprising to observe that the 10- to 20-year age group had the longest anesthetics and recovery times. As a large percentage of this group of patients underwent dental extraction with its aforementioned sequelae, there is a rational explanation for this finding. Furthermore, it was not the patients at the extremes of the age range that experienced the greatest rate of complications, as the majority of those patients with complications were in the 20- to 49-year age group.

Use of Premedication

The use of premedication in the ambulatory surgical patient is often a controversial issue. Many anesthesiologists believe that little or no premedication should be given because it may either be unnecessary or prolong the recovery period even to the point of admission to the hospital (1, 4, 5, 12). Others, however, feel that premedication may be in the best interest of good patient care. Clark and Hurtig (3) concluded that premedication with meperidine and atropine did not prolong recovery to street fitness after outpatient surgery. Furthermore, they (3) felt that the addition of preanesthetic medication offered the anesthesiologist a patient who was less anxious, would undergo a smoother and safer induction and maintenance, and would not have a prolonged recovery state.

The data in Table 4 show that the preoperative administration of hypnotic and tranquilizing drugs did not markedly prolong recovery whereas premedication with narcotics did. Thus, some premedicants can be given to ambulatory surgical patients without prolonging recovery.

Duration of Anesthesia

It has been suggested that the surgical procedures carried out in day care units be of short duration (less than 1 hour) in order that recovery periods no longer than 3 hours be achieved (1, 13). The findings in our study suggest that the length of anesthesia did not affect the length of the recovery period. Although there was approximately a 100-fold range in anesthesia times, there was only a 40% difference in recovery times. Furthermore, there was no correlation between the duration of anesthesia and recovery time. Procedures that resulted in hospital admission had a mean anesthesia time significantly longer than the population as a whole, yet the majority of those patients had an anesthesia time of less than 60 minutes. Therefore, placing an arbitrary upper limit on the duration of anesthesia does not seem to be indicated.

Effect of Anesthetic Agents

The notion that a specific anesthetic agent or technique is ideal for outpatient anesthesia is confusing at best (1, 2, 4–6, 12). In our study, patients receiving local anesthesia had a significantly shorter recovery period than those who received general anesthesia, and significantly fewer patients receiving local anesthesia were admitted to the hospital. This finding supports the views of those who feel that, when suitable, local anesthesia is preferred for ambulatory surgical patients (1).

Whereas there can be little disagreement that the anesthetic agents chosen for induction and maintenance in the ambulatory surgical patient should provide the safest induction possible, ideal surgical conditions, rapid recovery, and minimal postoperative morbidity (4), few authors agree on the specific anesthetic agent that will best provide these conditions (1, 2, 4–6, 12). In our study, no one general anesthetic technique appeared superior to any other.

Effect of Experience of 1 Year

Our retrospective study reveals that there is a statistically significant shorter recovery period for patients treated in 1980. As age, length of anesthesia, and anesthetic technique do not seem to affect the

duration of recovery, this might reflect the experience gained in postoperative management by our anesthesia and nursing personnel during the 1st year of operation of our self-contained ambulatory unit.

Morbidity

The number of patients requiring admission to the hospital in this study is comparable to the rate quoted for hospital-based, one-day surgical units (1). However, the percentage of hospital transfers is higher than that cited by free-standing centers (5, 14). The reason for this difference may reside in a bias built into the criteria for hospital transfer. Perhaps, free-standing centers transfer patients to the hospital for life-threatening complications only whereas hospital-based units might admit patients to the inpatient service with greater frequency for patient convenience, as well as for life-threatening complications.

In conclusion, it has been shown that ambulatory surgical care is appropriate for a wide variety of surgical procedures, patients of varying age who are A.S.A. physical status I or II, and a wide spectrum of anesthetic technique. Arbitrary limits placed on the age of the patient, duration of the procedure, and the use of premedication other than narcotics appear to be unwarranted as recovery appears to be governed primarily by the nature of the surgery.

ACKNOWLEDGMENTS

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Hemodynamic Effects of Intravenous Nitroglycerin: Importance of the Delivery System

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MUTCH, W.A.C., CULLIGAN, J. D., COTE, D. D., AND THOMSON, I. R.: Hemodynamic effects of intravenous nitroglycerin: Importance of the delivery system. Anesth Analg 1982;61:927–32.

Twenty patients about to undergo elective coronary artery bypass grafting entered a randomized double-blind trial comparing the hemodynamic effects of intravenous nitroglycerin (IV NTG) (0.5 µg/kg/min) (n = 9) versus placebo (n = 11). After a 20-min infusion period mean arterial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, central venous pressure, stroke index, and left ventricular stroke work index were significantly decreased by NTG. Cardiac index was unchanged despite a marked reduction of filling pressures, indicating improved ventricular function. The endocardial viability ratio (DPTI/SPTI) was improved by NTG, suggesting a favorable alteration of myocardial oxygen balance. Three additional patients received a larger dose of NTG (0.1 µg/kg/min). The hemodynamic effects were similar to, but more profound than, those noted at 0.5 µg/kg/min. The effects of IV NTG described here are compatible with a predominant venodilator effect of NTG and occurred at a dose previously reported to cause little or no hemodynamic change in a similar group of patients. We attribute the apparent increased potency of IV/NTG observed in our study to the use of an infusion system that does not adsorb NTG. Previous investigators have used infusion systems containing polyvinyl chloride (PVC) plastic, a substance that avidly adsorbs NTG. The resultant decrease in the administered dose of NTG renders dose-response data invalid when PVC-containing systems are used to deliver NTG.

Key Words: PHARMACOLOGY: nitroglycerin; SURGERY: cardiac; HEART: oxygen consumption, myocardial function.

ORGANIC NITRATES are of proven benefit in the treatment of patients with CAD (1–3). The precise mechanism by which nitrates relieve myocardial ischemia remains controversial, but administration usually results in a favorable alteration of the myocardial O_2 supply:demand ratio (4, 5). Intravenous NTG has been used for the treatment of intraoperative episodes of myocardial ischemia (6), and also for the prevention of ischemic episodes during the perioperative period, in patients with CAD (7). Accurate information regarding the hemodynamic effects of IV NTG in awake premedicated patients with stable angina pectoris would be of value to clinicians

wishing to begin a continuous infusion of IV NTG before the induction of anesthesia in patients with CAD. Intravenous NTG (1 µg/kg/min) has been reported to have little or no hemodynamic effect in awake premedicated patients with CAD (8). The latter information conflicts with our own clinical experience with IV NTG. Therefore, we designed a prospective, randomized, double-blind trial to compare the hemodynamic effects of IV NTG and placebo infusions in awake premedicated patients about to undergo elective CABG. Our study confirms our clinical impression that IV NTG has significant hemodynamic effects at low infusion rates.

Methods

Twenty patients about to undergo elective CABG entered a double-blind study comparing the hemodynamic effects of IV NTG versus placebo. Patients were assigned at random to receive IV NTG (0.5 µg/kg/min) (n = 9) or placebo (n = 11) infusion. All patients had stable angina pectoris and were receiving beta-adrenergic blocking agents and organic nitrates.

None of the patients were receiving calcium-channel blocking agents. Patients were fasting and had nitrates and beta-adrenergic blocking agents withheld from midnight prior to surgery. Normal ECG complexes were present in leads II and V_5 of all patients. The study was approved by the Committee on Human Experimentation of the University of Manitoba and informed consent was obtained from each patient. Premedication consisted of diazepam, 0.15 mg/kg, orally 90 minutes before surgery; morphine, 0.1 mg/ kg IM; and atropine, 0.007 mg/kg IM, 60 minutes before surgery. Nasal oxygen (3 L/min) was administered continuously following premedication. Upon arrival in the operating room, ECG leads II and CS_5 (9) were continuously monitored and recorded using a battery-operated Holter monitor (Del Mar Avion-

ics). Under local anesthesia, intravenous, radial arterial, and thermodilution pulmonary arterial catheters were inserted. Within 5 minutes of cannulation control hemodynamic measurements were made. All measurements were repeated following 20 minutes of IV NTG/placebo infusion. The investigators were unaware of whether NTG or placebo was being infused. Arterial pressure, pulmonary arterial pressure, PCWP, and CVP were recorded by a four-channel Hewlett-Packard polygraph (model 78304A) and transducers (model 1280). Thermodilution CO was measured in triplicate using an Edwards Laboratory Cardiac Output Computer (model 9520) with an injectate of 10 ml iced 5% dextrose in water. The computer-displayed CO values were used. The coefficient of variation of the CO measurements was ±7.7%. Derived hemodynamic variables included HR, CI, SI, SVRI, PVRI, RPP, and DPTI/SPTI ratio. The DPTI/SPTI ratio was determined by computerized planimetry of the arterial pressure trace; the average of three representative beats was used. Solutions of NTG were prepared by the hospital pharmacy from 0.6-mg tablets (Eli Lilly Company) dissolved in 0.9% sodium chloride. Nitroglycerin was administered by Sage pump (model 242) from a polypropylene syringe (Becton-Dickinson Company) with polyethylene tubing (Cobe Laboratories) directly connected to a Teflon catheter (Surgikos Company) in a peripheral vein. The recovery of NTG administered from this delivery system was assessed in vitro by ultraviolet spectrophotometry (10) and was found to be 99% during a 20-minute infusion period. Intragroup changes in hemodynamic variables were assessed using Student's t-test for paired data. Intergroup comparisons were made using Student's t-test for unpaired data.

The hemodynamic effects of IV NTG (1 µg/kg/ min) were assessed in three additional patients who received a 15-minute infusion.

Results

Patients given infusions of placebo and NTG did not differ significantly with respect to age, sex, LVEDP at the time of heart catheterization, ejection fraction, or total daily dose of beta-adrenergic blocking agents (Table 1). The majority of patients were receiving propanolol; however, one patient in each group was receiving nadolol and one patient given NTG was receiving timolol. One patient given placebo infusion had significant left main CAD. Before infusion of NTG or placebo, the groups did not differ significantly with respect to any hemodynamic variable, although the difference between groups for the CI

ABBREVIATIONS

BSA	body surface area
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CI	cardiac index
CO	cardiac output
CVP	central venous pressure
DAP	diastolic arterial pressure
DPTI/SPTI	diastolic pressure time index/systolic pressure time index
ECG	electrocardiogram
HR	heart rate
LVEDP	left ventricular end diastolic pressure
LVSWI	left ventricular stroke work index
MAP	mean arterial pressure
MDP	mean diastolic pressure
MPAP	mean pulmonary artery pressure
MSP	mean systolic pressure
NTG	nitroglycerin
PCWP	pulmonary capillary wedge pressure
PVC	polyvinyl chloride
PVRI	pulmonary vascular resistance index
RPP	rate-pressure product
SAP	systolic arterial pressure
SI	stroke index
SVRI	systemic vascular resistance index
T_D	diastolic time
T_S	systolic time

DERIVED HEMODYNAMIC PARAMETERS

BSA	height $(cm)^{0.725} \times$ weight $(kg)^{0.425} \times 71.84 \times 10^{-4}$
CI	CO/BSA
DPTI/SPTI	$[(MDP - PCWP) \times T_D]/MSP \times T_S$
PVRI	$[(MPAP - PCWP)/CI] \times 79.9$
RPP	HR × SAP
SI	CI/HR
SVRI	$[(MAP - CVP)/CI] \times 79.9$

approached statistical significance (p = 0.054) (Table 2). Following 20 minutes of NTG/placebo infusion, significant differences were noted between groups. Values for MAP, MPAP, PCWP, CVP, and CI were significantly lower following NTG ($p \le 0.05$). The DPTI/SPTI ratio was significantly higher with NTG. There was no difference noted between groups in HR, SI, LVSWI, SVRI, PVRI, or RPP.

Significant hemodynamic changes were also noted among patients given NTG. Mean arterial pressure, MPAP, PCWP, CVP, SI, and LVSWI decreased significantly after 20 minutes of NTG infusion. The DPTI/SPTI ratio increased significantly. No change in HR, CI, SVRI, or RPP was noted. The placebo infusions were associated with small but statistically significant increases in HR and RPP.

Data from three patients who received 1.0 μg/kg/min of IV NTG for 15 minutes are presented in Table 3. The changes in this small group were qualitatively similar to, but more profound than, those observed at

the 0.5 μg/kg/min dose. Mean pulmonary arterial pressure and PCWP decreased to 6.3 ± 3.0 torr and 2.3 ± 1.9 torr, respectively. A significant decrease in SVRI also occurred in these three patients. In one patient, PCWP decreased from 9 to 1 torr and CVP from 5 to 0 torr. These changes were associated with a 25% decrease in MAP and a 25% increase in HR. When anesthesia was subsequently induced and positive pressure breathing instituted, further hypotension and tachycardia occurred and ECG changes of myocardial ischemia were precipitated. Because of these adverse events we considered it unethical to study further patients at the 1.0 μg/kg/min dose of IV NTG.

Discussion

When administered at 0.5 μg/kg/min, IV NTG appeared primarily to cause an increase in venous

TABLE 1

Patient Data for NTG (n = 9) and Placebo (n = 11) Groups*

	NTG	Placebo
Age (yr)	63.7 ± 3.2	56.2 ± 2.3
Weight (kg)	82.4 ± 3.4	83.7 ± 2.1
LVEDP at heart catheterization (torr)	16.0 ± 1.3	15.6 ± 1.3
Ejection fraction (%)	63.6 ± 5.0	62.4 ± 4.0
Total dose of beta-adrenergic blocker (mg of propanolol/day)	147.8 ± 24.2	188.0 ± 36.3

* Values are means ± SEM. No significant differences existed between groups. Daily dose of all beta-adrenergic blocking agents is expressed as an equivalent dose of propanolol.

TABLE 3

Hemodynamic Data in Preinfusion Period and after 15 Minutes of IV NTG (1 μg/kg/min) Infusion (n = 3)*

	Preinfusion	15 min
HR (beats·min^{-1})	63.7 ± 2.2	81.0 ± 6.7
MAP (torr)	96.0 ± 2.1	85.0 ± 6.8
MPAP (torr)	15.0 ± 3.2	6.3 ± 3.0†
PCWP (torr)	9.7 ± 1.2	2.3 ± 1.9†
CVP (torr)	4.7 ± 2.6	1.7 ± 1.7
CI (L·min^{-1}·m^{-2})	2.81 ± 0.17	2.81 ± 0.38
SI (ml·m^{-2})	44.1 ± 2.4	34.4 ± 2.5†
SVRI (dynes·sec·m^2·cm^{-5})	2621.4 ± 225	2429.6 ± 241.2†
PVRI (dynes·sec·m^2·cm^{-5})	147.2 ± 5.2	109.4 ± 19.7
RPP	9098.3 ± 728.7	10863.0 ± 1468.7

* Values are means ± SEM.
† $p \le 0.05$ by Student's t-test for paired data.

TABLE 2

Hemodynamic Data in Placebo (n = 11) and IV NTG (0.5 μg/kg/min) (n = 9) Groups in Preinfusion Period and following Infusion for 20 Minutes*

	Preinfusion		20 min	
	Placebo	NTG	Placebo	NTG
HR (beats·min^{-1})	64.6 ± 2.3	60.9 ± 4.2	70.4 ± 2.2‡	65.3 ± 4.3
MAP (torr)	101.5 ± 3.6	106.1 ± 4.8	105.7 ± 3.1	93.0 ± 4.7†‡
MPAP (torr)	22.8 ± 2.5	20.8 ± 2.7	23.1 ± 2.7	13.6 ± 1.7†‡
PCWP (torr)	13.2 ± 1.9	13.6 ± 1.3	14.7 ± 2.7	7.7 ± 1.2†‡
CVP (torr)	6.8 ± 1.3	7.9 ± 1.5	6.8 ± 1.0	3.6 ± 1.0†‡
CI (L·min^{-1}·m^{-2})	2.83 ± 0.16	2.42 ± 0.10	2.90 ± 0.16	2.38 ± 0.14†
SI (ml·m^{-2})	43.6 ± 2.2	40.3 ± 1.3	41.3 ± 2.4	36.9 ± 2.1‡
LVSWI (g·m·m^{-2}·beat^{-1})	53.1 ± 2.5	51.0 ± 3.4	51.7 ± 2.1	43.6 ± 4.6‡
SVRI (dynes·sec m^2 cm^{-5})	2757 ± 186	3276 ± 189	2841 ± 229	3025 ± 132
PVRI (dynes·sec·m^2·cm^{-5})	275.4 ± 30.9	234.9 ± 15.7	244.4 ± 24.6	200.5 ± 26.4
RPP	9699 ± 572	9672 ± 797	10760 ± 519‡	9440 ± 804
DPTI/SPTI	0.99 ± 0.07	1.16 ± 0.11	0.91 ± 0.07	1.34 ± 0.11†‡

* Values are means ± SEM.
† $p \le 0.05$ versus placebo by Student's t-test for unpaired data.
‡ $p \le 0.05$ versus preinfusion period by Student's t-test for paired data.

capacitance manifested by a decrease in CVP and PCWP. This large decrease in preload was associated with a significant, but comparatively small, reduction in SI. Cardiac index was unchanged by NTG, indicating a significant improvement in overall pumping function of both right and left ventricles when assessed in terms of conventional ventricular function curves (11). This contention is further supported by the lack of significant differences in SI or LVSWI between NTG and placebo after 20 minutes of infusion (Figure). This tendency for CI to be maintained despite significant decreases in right and left heart filling pressures is typical of NTG effect (3, 12), and requires explanation. As HR did not change significantly with NTG, the improved ventricular function must be related to changes in impedance to ventricular ejection (13), improved myocardial contractility (14), or alteration of the diastolic pressure-volume characteristics of the heart (15). Both MPAP and MAP decreased significantly with NTG, indicating that impedance to ejection decreased for both ventricles, especially the right, and probably contributed to the improved ventricular function. Nitroglycerin does not directly influence myocardial contractility (3–5), but might indirectly have influenced contractility by improving oxygen delivery to ischemic myocardium (16). A baroreflex-mediated change in myocardial contractility with NTG seems unlikely in view of the insignificant change in HR.

Alteration of the diastolic pressure-volume characteristics of the left ventricle may explain much of

the observed alteration of left ventricular function during infusion of NTG. Ludbrook et al (17) observed a parallel downward and rightward displacement of the left ventricular diastolic pressure-volume relationship after sublingual NTG was administered to a group of patients with CAD undergoing diagnostic heart catheterization. No changes occurred in the passive elasticity or the time constant ("T") of relaxation of the left ventricle. They attributed the alteration in diastolic pressure-volume characteristics of the left ventricle to a decrease in external constraint related to reduction of right ventricular diastolic loading. Similar changes in diastolic ventricular function have been noted with sodium nitroprusside (18). Although changes in diastolic function of the left ventricle are likely secondary to changes in right ventricular preload, this view has been challenged by Brown et al (16) who observed that low-dose intracoronary NTG caused a reduction in left heart filling pressures in the absence of any systemic hemodynamic changes in a group of 11 patients with CAD and segmental left ventricular wall motion abnormalities. They attributed the observed reduction in left heart filling pressure to improved coronary blood flow related to the significant coronary artery stenosis dilation observed in their study.

Whatever the mechanism of the reduced PCWP observed in our patients given NTG, it resulted in a marked passive reduction in MPAP which must have reduced right ventricular impedance remarkably, perhaps explaining most of the improvement in right ventricular function.

Intravenous NTG (0.5 μg/kg/min) appeared to exert little effect on arteriolar resistance vessels as neither SVRI or PVRI changed significantly. The etiology of the decrease in MAP with NTG is somewhat unclear in view of the statistically insignificant changes in both CI and SVRI. A passive decrease in MAP secondary to the reduction in CVP should have occurred, but is insufficient in magnitude to explain all the observed change in MAP. The combined variability of CI and MAP measurements may explain the lack of a statistically significant decrease in SVRI. The observed difference in CI with placebo and with NTG after 20 minutes of placebo/NTG infusion also requires explanation. In fact, the difference between groups approached statistical significance during the preinfusion period ($p = 0.054$), and the finding of statistical significance after 20 minutes of infusion is likely fortuitous and reflects only insignificant additional changes. The percent change from control of

FIGURE. Effect of nitroglycerin on left ventricular function. Mean stroke index (SI) ± SEM is plotted against mean pulmonary capillary wedge pressure (PCWP) ± SEM after 20 minutes of NTG or placebo infusion, respectively. Despite significantly lower PCWP with NTG ($p \leq 0.05$, Student's t-test), SI did not differ significantly between groups, indicating superior left ventricular function with NTG.

CI did not differ between groups after 20 minutes of placebo/NTG infusion.

Intravenous NTG (0.5 µg/kg/min) appeared to alter favorably the myocardial oxygen supply:demand ratio. This was evident from the increase in the ratio of diastolic to systolic pressure time indices (DPTI/SPTI) noted with NTG (19). The improvement in this "endocardial viability ratio" was the result of favorable alteration of both supply and demand terms of the ratio related to reductions in systolic arterial pressure and PCWP, respectively. The direct coronary artery vasodilator properties of NTG also tend to influence favorably the myocardial oxygen supply: demand ratio (16).

In contrast to the effects of 0.5 µg/kg/min of IV NTG, the data from three patients who received 1.0 µg/kg/min suggest a more marked hemodynamic response. The reduction in preload in this group was comparatively profound, and a significant decrease in SVRI was observed. The marked decrease in preload combined with a decrease in SVRI has the potential to cause serious hypotension, especially if other interventions are superimposed. One of the three patients developed hypotension, tachycardia, and ECG evidence of myocardial ischemia subsequent to anesthetic induction and institution of positive pressure ventilation, during continuous NTG infusion at 1.0 µg/kg/min.

In this study, patients in both groups were similar and appeared to be drawn from the same population. Randomization of patients into placebo and NTG groups eliminates time as a confounding variable. Thus, hemodynamic differences between groups after 20 minutes of infusion should represent true drug effects. The delivery system used in our study adsorbed insignificant quantities of NTG when assessed in vitro. The plasma half-life of NTG in humans has been reported as 1.9 and 2.6 minutes (20, 21). As we infused NTG for a 20-min period, a steady-state plasma level should have been achieved (22). Thus, we are confident that the dose-response data reported here are accurate. Nonetheless, caution should be exercised in the interpretation of these results. Several factors may have tended to accentuate the observed response to IV NTG. Overnight fasting without maintenance IV fluids may have caused a mild degree of hypovolemia before NTG infusion. Many patients were taking long-acting nitrate preparations that were withheld during the period of fasting. If a nitrate withdrawal syndrome occurred (23), it might have elevated the level of venomotor tone before IV NTG

infusion, consequently accentuating the response. The data remain applicable when NTG is infused under the same circumstances as in this investigation.

The substantial hemodynamic effects observed in this study occurred at a relatively low NTG infusion rate. Landry et al. (8) found that an infusion of IV NTG (1.0 µg/kg/min) had minimal hemodynamic effects in seven awake premedicated patients with CAD about to undergo CABG. An 11.2% decrease in PCWP was the only significant change noted in their study. The discrepancy between their results and our own is probably related to differing methods of NTG administration. Landry et al (8) infused NTG through a PVC administration set (D. Philbin, personal communication, 1981). Nitroglycerin is avidly adsorbed to the PVC plastic contained in most standard intravenous bags and tubing (24). Insignificant adsorption of NTG occurs with the delivery system used in our study. This would result in a marked difference in the dose of NTG administered in the two studies. The presence of PVC tubing at any point between the NTG source and the patient results in the administration of reduced concentrations of NTG. The administered concentration also changes with time as the PVC becomes saturated with NTG. The actual concentration administered depends on the surface area of the PVC tubing and the infusion flow rate (25). Intravenous NTG is usually infused centrally. Commonly used CVP, pulmonary artery, and introducer catheters also contain varying lengths of PVC plastic. We have found in vitro that these catheters cause further significant NTG adsorption (unpublished observations). These factors may explain the relatively high doses of NTG required by other investigators to produce significant hemodynamic effects during perioperative IV NTG administration (26–29). The appearance of commercially available nonadsorptive NTG delivery systems similar to ours (Nitrostat IV, Parke Davis; Tridil, American Critical Care) raises the possibility of inadvertent NTG overdosage if previously published infusion rates are used with these systems.

When administered via a nonadsorptive system which excluded PVC, low-dose IV NTG (0.5 µg/kg/min) caused significant hemodynamic effects. A predominant venodilator effect, as well as an improvement in ventricular function, was noted in awake premedicated patients about to undergo CABG. These hemodynamic effects combined with direct effects of NTG on the coronary circulation may result in a more favorable myocardial oxygen supply:demand ratio

before induction of anesthesia when IV NTG is administered to patients with CAD.

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Premedication with Intramuscular Midazolam: A Prospective Randomized Double-Blind Controlled Study

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One hundred A.S.A. physical status I and II surgical patients were randomized to receive midazolam, 0.07 mg/kg (group M, 31 patients), hydroxyzine, 1.0 mg/kg (group H, 34 patients), or midazolam diluent as a placebo (group P, 35 patients). Drugs were administered in the vastus lateralis muscle 60 to 90 minutes before anesthesia induction. Anesthesia was induced with thiopental, 3.0 mg/kg, followed by 1.0-mg/kg increments if required. An entry criterion was that patients score ≥50% on a subjective Anxiety Visual Analog Test (AVAT). Anxiety was also objectively rated on a six-point scale by a trained observer. Patients and observer were unaware of type of premedication used. Midazolam and hydroxyzine produced significantly ($p < 0.05$) greater reduction of anxiety than placebo on both the AVAT and objective anxiety evaluations. Peak onset appeared between 30 and 60 minutes after drug administration. Hemodynamic changes were similar in all groups, and no untoward reactions were encountered before anesthesia. The injection site 24 and 48 hours after administration showed evidence of mild tissue irritation in 68% of patients in group H, 26% of patients in group M, and none of the patients in group P. Midazolam is an efficacious, safe premedicant in relatively healthy patients. It has a prompt onset of action with only minimal tissue irritation.

Key Words: PREMEDICATION: midazolam; HYPNOTICS: benzodiazepines, midazolam.

MIDAZOLAM is an imidazobenzodiazepine the pharmacology of which has been shown in animals to be similar to other 1-4-benzodiazepines (1). It has been used clinically for intravenous induction of anesthesia (2–6). It has hypnotic, anxiolytic, and amnestic properties that make it suitable for preanesthetic medication. Intravenous midazolam produces satisfactory premedication (3). The purpose of this investigation was to determine the safety and efficacy of intramuscular midazolam used for preoperative sedation. To accomplish this purpose, midazolam was compared with an active compound, hydroxyzine, and placebo using a double-blind randomized experimental design.

Methods

Patients in A.S.A. physical status I or II scheduled for elective surgery composed the study population. One hundred patients were randomly assigned to one of three premedication groups (Table 1). Patients with a subjective anxiety score of ≥50% on an Anxiety Visual Analog Test (AVAT) were eligible for participation in the investigation. The AVAT is a visual analogue quantitative measure of anxiety (Figure). To determine the AVAT score, patients are given a sheet of paper with a 100-mm length line and asked to rate their anxiety along the line (from 0 to 100 mm). Of 233 patients screened, 133 (57%) were excluded because their AVAT score was less than 50. Also excluded were patients who had a history of drug abuse and/or chronic hypnotic, tranquilizer, and narcotic therapy. All patients gave informed consent, and the investigation was approved by the Institutional Review Board of the University of Alabama in Birmingham.

Test drugs were administered 60 to 90 minutes before anesthesia. All medications were given with a 4-cm, 22-gauge needle in the vastus lateralis muscle.

Patients in group M received 0.07 mg/kg of midazolam hydrochloride (5 mg/ml), those in group H received hydroxyzine 1.0 mg/kg (50 mg/ml), and those in group P midazolam diluent in a volume equal to

TABLE 1

Three Premedication Experimental Groups

Group	Age	Sex (M/F)	Weight	Drug dose
	yr		kg	
Midazolam (n = 31)	31 ± 1.7	5/26	75 ± 4.2	0.07 mg/kg IM
Hydroxyzine (n = 34)	30 ± 1.8	3/31	70 ± 3.3	1.0 mg/kg IM
Placebo (n = 35)	36 ± 1.8	9/26	71 ± 2.4	Midazolam vehicle†

* Values are means ± SD.
† Volume of injection equal to that of midazolam group.

ANXIETY RATING SCALE

INSTRUCTIONS: WE WOULD LIKE TO ESTIMATE YOUR PRESENT LEVEL OF ANXIETY REGARDING YOUR UPCOMING OPERATION. THE BOTTOM OF THE LINE REPRESENTS NO ANXIETY AT ALL AND THE TOP OF THE LINE THE HIGHEST ANXIETY YOU CAN IMAGINE. PLEASE MAKE A MARK AT THE LEVEL YOU PRESENTLY FEEL RIGHT NOW.

YES, VERY MUCH SO

NO, NOT AT ALL

FIGURE. Anxiety Visual Analog Test (AVAT) used to quantitate subjective anxiety. Line is 100 mm in length. Patients are told to mark line at point at which they feel their anxiety level rests. Instructions for marking anxiety level are printed above line.

that given to patients in group M. Anesthesia in all patients was induced with thiopental, 3.0 mg/kg IV (25 mg/ml), followed by 1.0-mg/kg incremental doses if the first and subsequent doses did not induce anesthesia. Criteria for anesthesia induction were all of the following: loss of response to verbal commands, loss of eyelid reflex, and loss of voluntary movement.

Patients were observed before drug administration, 15, 30, 45, and 60 minutes after drug administration, during anesthetic induction, during emergence from anesthesia, and 24 and 48 hours after surgery. The double-blind study design consisted of a floor nurse administering a known drug to patients who were unaware of which drug was administered, combined with observations that were made by a different trained nurse observer who was unaware of the medication administered. Measurements in the preoperative period included systolic, diastolic, and mean blood pressures, heart rate, and objective evaluation of sedation. The objective assessment of sedation consisted of classification of patients into one of six groups: hyperactive, awake/alert, awake but drowsy, asleep but easily arousable, asleep and difficult to arouse, and asleep and not arousable by verbal commands. These six categories were assigned a numerical value from 1 (asleep/no response) to 6 (hyperactive). AVAT was performed the night before surgery, just prior to premedication, 60 minutes before premedication and/or just before the patient was transferred to the operating room. The observation made before transfer to the operating room was defined as the last observation. The time required for anesthesia induction and amount of thiopental needed were recorded. Postoperative nausea and vomiting were noted and the injection site was evaluated 24 and 48 hours after premedication.

Statistical analysis included computation of mean values for variables in each group. Analysis of variance or covariance was used to compare groups and

TABLE 2

Blood Pressure (BP) and Heart Rate (HR) after Premedication*

	Group M			Group H			Group P		
	n	BP	HR	n	BP	HR	n	BP	HR
Before medication	30	92 ± 2.3	79 ± 1.8	33	91 ± 2.4	77 ± 2.1	34	89 ± 1.9	76 ± 2.2
15 min†	30	88 ± 2.0	78 ± 1.8	33	92 ± 2.0	76 ± 1.9	34	88 ± 1.8	76 ± 1.9
30 min	29	88 ± 1.8	75 ± 1.8	32	91 ± 2.3	73 ± 2.0	32	90 ± 1.7	75 ± 2.0
45 min	30	93 ± 1.9	87 ± 2.6	33	95 ± 2.3	81 ± 1.8	34	95 ± 1.9	82 ± 2.4
60 min	25	90 ± 2.8	80 ± 2.6	30	89 ± 1.9	78 ± 2.3	28	92 ± 2.5	82 ± 2.3

* Values are means ± SD; n = number of patients.
† Minutes after administration of drug or placebo.

determine statistically significant ($p < 0.05$) differences. A one-sided test was used for the placebo comparison and two-sided tests were used for active drug comparisons. Fischer's exact test was used for comparison among groups of the incidence of apnea, nausea, vomiting, and quality of sedation.

Results

The three groups were similar with regard to age, sex, weight (Table 1), and race. Blood pressure and heart rate values were the same in each group at each observation period (Table 2). There was no confusion, restlessness, tremor, nausea, or apnea in any patient from the time of premedication until the time of induction. There were differences among the groups in terms of objective degree of sedation (Table 3). The mean base line values were similar in all groups, but midazolam produced significantly ($p < 0.01$) better sedation than placebo. Midazolam also produced significantly ($p \leq 0.02$) lower scores (better sedation) than hydroxyzine at the 15, 30, and 60-minute observation periods. The results of AVAT are shown in Table 4. The base line values were similar in all groups, but midazolam produced significantly ($p < 0.01$) better scores than placebo at the last observation and at the 60-minute period. Midazolam was also

significantly ($p = 0.04$) superior to hydroxyzine at the 60-minute observation period, but not different at the last observation. Both drugs were superior to placebo at the last observation period. In groups M and H satisfactory sedation scores were significantly ($p < 0.01$) different from group P. The time for anesthesia induction was significantly ($p < 0.02$) shorter in groups M (54 ± 36.2 seconds) and H (45 ± 26.7 seconds) than group P (73 ± 45.1 seconds). The induction dosage of thiopental was also significantly ($p < 0.05$) less in groups M (3.2 ± .54 mg/kg) and H (3.1 ± 0.58 mg/kg) than in group P (3.6 ± 0.89 mg/kg). Although not significantly different ($p = 0.20$),

TABLE 4

Subjective Degree of Sedation after Premedication: Anxiety Visual Analog*

	Midazolam	Hydroxyzine	Placebo
Control (96)	61 ± 22.8 (28)	66 ± 23.5 (31)	52 ± 28.3 (32)
Last observation (96)	35 ± 21.4† (28)	44 = 28.7† (31)	51 ± 27.7 (32)
+60 min (%)	29 ± 20.1†‡ (15)	46 ± 30.1 (21)	49 ± 24.9 (22)

* Where % = percent anxiety. Values are means ± SD. Number of patients is shown in parentheses.
† $p < 0.01$ versus placebo.
‡ $p < 0.02$ versus hydroxyzine.

TABLE 3

Objective Degree of Sedation after Premedication

Interval	Mean ± SD	Degree of Sedation*						No. of patients
		6	5	4	3	2	1	
Midazolam								
Base line	5.0 ± 0.37	2	26	2	0	0	0	30
15 min	4.6 ± 0.73†‡	0	21	5	4	0	0	30
30 min	3.9 ± 0.70†‡	0	6	15	8	0	0	29
45 min	3.9 ± 0.70†	0	3	18	5	1	0	27
60 min	3.5 ± 0.63†‡	0	0	9	6	1	0	16
Hydroxyzine								
Base line	5.0 ± 0.17	0	32	1	0	0	0	33
15 min	5.0 ± 0.30	1	30	2	0	0	0	33
30 min	4.4 ± 0.50†	0	13	18	0	0	0	31
45 min	3.9 ± 0.60†	0	4	20	7	0	0	31
60 min	3.9 ± 0.58†	0	3	16	5	0	0	24
Placebo								
Base line	4.9 ± 0.45	1	29	2	2	0	0	34
15 min	4.9 ± 0.38	0	32	1	1	0	0	34
30 min	4.9 ± 0.43	0	28	2	1	0	0	31
45 min	4.9 ± 0.56	1	27	1	2	0	0	31
60 min	4.9 ± 0.60	2	18	2	1	0	0	23

* Numerical designations are: 6, hyperactive; 5, awake and alert; 4, awake and drowsy; 3, asleep/easily responds to verbal command; 2, asleep/difficult to respond to verbal command; 1, asleep/no response to verbal command.
† $p < 0.01$ versus placebo.
‡ $p < 0.02$ versus hydroxyzine.

TABLE 5

Evidence (%) of Tissue Irritation at Injection Site after 24 and 48 hours

	Midazolam	Hydroxyzine	Placebo
Pain	26*	68†	0
Erythema	0	6	0
Induration	0	6	0
Swelling	0	9	0

* $p < 0.01$ versus hydroxyzine and placebo.
† $p < 0.01$ versus placebo.

there was a trend toward more frequent apnea during anesthesia induction in group M (52%) and group H (50%) than in group P (33%).

After surgery, patients in group H (26%) had a significantly ($p < 0.05$) lower incidence of nausea than patients in group M (54%). The incidence of nausea in patients in group P was 44%. The incidence of vomiting was similar in all three groups of patients (group M 21%, group H 10%, and group P 20%). Evaluations of injection sites 24 and 48 hours after drug administration are shown in Table 5. The incidence of pain at the injection site, the same at 24 and 48 hours after injection, was greatest in group H (68%), absent in group P, and 26% in group M. The incidence of pain was significantly ($p < 0.01$) greater in group H than in group M. There was a 6% incidence of erythema and induration in patients given hydroxyzine and an incidence of swelling of 9% in that group.

Discussion

Premedication traditionally has several goals: reduction of anxiety, pain, and secretions, and provision of basal or background sedation. Of these, the primary purpose of prescribing drugs in the immediate preoperative period is to allay patient anxiety. Midazolam is a hypnotic with anxiolytic properties which has been used intravenously for preoperative medication (3). Our study was designed so that both the patient and observer were unaware of the medication (double-blind). Randomization produced groups with similar demographic characteristics and all patients received the same visits, tests, and treatments.

The results demonstrate that midazolam may be safely given intramuscularly to produce satisfactory premedication. Intravenous midazolam can produce respiratory depression (7–10), but our study did not use tests sensitive enough to detect this potential adverse effect. The degree of respiratory depression from intramuscular midazolam has not been deter-

mined, but presumably it should be similar to the respiratory depression associated with intravenous midazolam as similar blood levels may be attained (11). Also, it is important to realize that the present investigation included relatively young, healthy patients and the safety of midazolam in older, more ill patients has not been demonstrated.

Midazolam and hydroxyzine proved to be effective anxiolytic drugs. Patients had high preoperative anxiety levels (>50% AVAT scores), and both compounds were clearly superior to placebo in reducing preoperative anxiety. Midazolam proved to be slightly superior to hydroxyzine in terms of subjective (AVAT) (Table 4) and objective scoring (Table 3) of sedation. Fragen and co-workers (12) have reported preliminary data also demonstrating efficacy of midazolam for intramuscular premedication. In that study, using slightly higher doses of midazolam (0.075 mg/kg) and hydroxyzine (1.5 mg/kg) in smaller groups of patients, midazolam and hydroxyzine were superior to placebo in anxiolytic effects. Additionally, in the same study, Fragen et al (12) demonstrated that intramuscular midazolam caused significantly greater lack of recall than either hydroxyzine or placebo 30 minutes after premedication. We did not investigate the amnestic properties of the drugs in this study.

The preoperative interview itself is known to have a calming effect (13). Indeed, some anesthesiologists subscribe to a pharmacologic nihilism, feeling that proper preanesthetic interview, examination, and consultation obviate the need for preoperative anxiolytic drug therapy. The present findings demonstrate clearly that despite identical preoperative visits, the active compounds, midazolam and hydroxyzine, proved significantly superior to placebo in reducing patient anxiety. In our experimental setting, the effect on anxiety of the preoperative interview per se was not examined.

Of particular interest was the rapidity of onset of sedative action associated with midazolam. Fifteen minutes after premedication, midazolam had significantly reduced the objective ratings of anxiety from a score of 5.0 to 4.5 with the peak effect measured at 60 minutes. With both active drugs a time-response effect pattern emerged, both drugs producing progressive effect as time elapsed, whereas the anxiety remained constant in patients given placebo injections (Table 3). The pharmacodynamic measures of drug activity (anxiety levels) are consistent with the pharmacokinetic studies. Amrein and co-workers (14), for example, demonstrated in six subjects rapid absorption of midazolam following intramuscular adminis-

tration with peak blood levels after 30 minutes. The rapid absorption of intramuscular midazolam contrasts to the more variable absorption of another 1-4-benzodiazepine, diazepam (15-17), when given intramuscularly. The vastus lateralis muscle, the site of administration in the present study, is known to influence favorably the absorption of intramuscular benzodiazepines (16).

The postoperative evaluation of the injection site revealed minimal tissue reaction to midazolam (group M) and midazolam vehicle (group P). This is not surprising as laboratory evidence reveals that midazolam produces little tissue reaction (18), and this confirms the findings of Fragen et al, who also administered midazolam intramuscularly (0.075 mg/kg) (12). Water solubility of midazolam occurs only at a pH <4.0 (1), but the acid vehicle is nonirritating to the muscle.

Postoperative nausea was more prevalent in patients given placebo injections and in patients given midazolam than in patients receiving hydroxyzine. This probably reflects the known antiemetic effect of hydroxyzine (19), as all patients received similar anesthetic drugs and postoperative analgesics. The incidence of nausea was similar after placebo and midazolam, which indicates that midazolam has no antiemetic action. There was no nausea or vomiting before anesthesia in any group.

In summary, patients premedicated with intramuscular midazolam and hydroxyzine are better sedated than are patients given placebo injections. The sedation results in lower anesthesia induction requirements. There are no untoward side effects associated with midazolam and hydroxyzine except for a tendency toward more apnea during induction. Midazolam is a safe and effective premedicant when given intramuscularly in relatively young, healthy patients.

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Effect of Nitrous Oxide Solubility on Vaporizer Aberrance

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Concentrations of halogenated anesthetics produced by contemporary vaporizers vary from vaporizer dial settings when carrier gas is not 100% oxygen. This effect is most marked when carrier gas changes from 100% O_2 to 100% nitrous oxide (N_2O). Vapor concentrations of halothane and enflurane from vaporizers with 6 L/min carrier gas flows were reduced to 3% from 4% until absorption of N_2O by the liquid anesthetic ceased. Presaturation of liquid anesthetics with N_2O eliminated the transient decrease of vapor output. Steady-state outputs of halothane and enflurane in 100% N_2O were 10% below dial settings. The significance of these changes in administration of closed-circuit anesthesia with an out-of-circuit vaporizer is discussed.

Key Words: EQUIPMENT: vaporizers.

USING a flow-over vaporizer for the quantitative practice of closed-circuit anesthesia ideally requires that output concentrations of halogenated anesthetics predictably correspond to the volume-percentage setting of the vaporizer dial. These vaporizer settings are calibrated with air as the carrier gas. Although vaporizer output is accurate over a wide range of O_2 flow rates (1), changing the percentage of N_2O in the carrier gas causes significant variation in vaporizer performance.

We suggest how the solubility of N_2O in the halogenated anesthetic liquid and the viscosities of different carrier gases inside the vaporizer can separately contribute to variation of vapor concentration output from vaporizers.

Methods

Eight North American Dräger anesthesia machines equipped with Vapor 19 halothane and enflurane vaporizers and four Ohio anesthesia machines with Ohio halothane and enflurane vaporizers were studied. Gas composition was measured directly at the gas outlet from the machine by a Perkin-Elmer model 1100 mass spectrometer. A Hewlett-Packard 5840A

gas chromatograph was also used to measure concentrations of volatile anesthetics sampled at the same site. Gas concentrations were continually recorded by an Omega chart recorder.

The halothane vaporizer was set at the maximum of 4%, with a 6 L/min O_2 flow (Figure, a). Oxygen flow was then turned off and a 6 L/min N_2O flow was turned on (Figure, b) and continued until a stable vapor concentration was measured. N_2O flow was then turned off and oxygen flow restored (Figure, c). Next, the halothane was drained from the vaporizer. This halothane was saturated with N_2O by bubbling N_2O through the liquid halothane while agitating it. The vaporizer was flushed with N_2O and then refilled with the N_2O saturated halothane, poured openly into the filling spout. A flow of N_2O at 6 L/min was begun (Figure, d). For this illustration only, an Engström EMMA gas analyzer was used. It was calibrated against the mass spectrometer and gave readings in agreement with vaporizer dial settings, with oxygen as carrier gas. The same protocol was used for the enflurane vaporizers. Statistical analysis of results was made by Student's paired t-test.

Results

All vaporizers showed the same pattern of a transient decrease in vapor concentration, when the carrier gas was switched from O_2 to N_2O (Figure, a and b). Nadir was reached in 8 seconds. At 6-L/min carrier gas flows, stable "plateau" vapor concentrations were
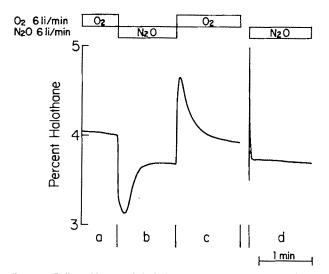
FIGURE. Dräger Vapor 19 halothane concentration with alternating carrier gas flows (see "Methods"). In gap between c and d halothane is drained from vaporizer, presaturated with N₂O, and refilled.

TABLE

Vapor Plateau Concentrations after Changing Carrier Gas from O₂ to N₂O*

	Dial setting	
	4 vol% halothane	4 vol% enflurane
Dräger Vapor 19	3.48 ± 0.07† (decrease 12%)	3.74 ± 0.10† (decrease 7%)
Ohio	3.50 ± 0.20‡ (decrease 10%)	3.38 ± 0.11§ (decrease 13%)

* Values are means ± SD.
† $p < 0.001$.
‡ $p < 0.02$.
§ $p < 0.01$.

produced after 1 minute. These new concentrations could be continually maintained, until all liquid anesthetic was vaporized. The Dräger Vapor 19 halothane vaporizers set at 4% reestablished a halothane-in-N₂O output at only 3.48% by volume. Similar reductions were seen from the other vaporizers subjected to this maneuver (Table).

The values in the Table were the same when measured by either a mass spectrometer or a gas chromatograph.

In separate experiments when O₂ flow followed N₂O (Figure, c) the vapor concentrations increased to and reached zenith in 4 seconds. Concentrations then returned to original (Figure, a) outputs, slightly varying from the vaporizer dial setting, presumably because of imperfect temperature compensation (drift).

Presaturation of halothane with N₂O prevented the transient decrease in vapor concentration (Figure, b)

when N₂O flow was again begun (Figure, d). Instead, steady-state vaporizer output of halothane was instantaneously achieved. The momentary surge of vapor output at the beginning of section d in the Figure represents the release of some dissolved N₂O from halothane liquid into the vaporizing chamber, into which ambient air had leaked during vaporizer refilling. Presaturation of enflurane with N₂O similarly abolished the transient decrease in concentration of vaporizer output occurring from a direct switch from O₂ to N₂O.

Discussion

Various investigators (1–4) have drawn different conclusions concerning vaporizer performance under conditions of low flows of carrier gas. Our basic findings (Table) are in qualitative agreement with measurements reported by Diaz (2) and Lin (1). High flow rates of carrier gas were used in our studies to determine the final vaporizer output plateaus. Low flows of different carrier gases can greatly prolong the discrepancy between vaporizer dial settings and actual vapor concentrations (reference 1, see figure 6). Thus, if a halogenated agent were to be introduced by a vaporizer to a closed-circle system at a time of low flows of N₂O, adequate concentrations of halogenated vapor could not be generated from the vaporizer, despite appropriate dial settings. This problem would be especially prominent if 100% O₂ had previously passed through the vaporizer.

The phenomenon of initial marked decrease in vaporizer output (Figure, b, 1st minute) occurred because N₂O dissolved into the halogenated liquid. The solubility of N₂O in halothane, enflurane, and isoflurane is approximately 4 ml of N₂O per milliliter of halogenated anesthetic, as recently has been determined with a Van Slyke manometric apparatus (5).

When saturation of halothane by N₂O within the vaporizer was complete (Figure, b, plateau) the vapor concentrations did not return to original values. With N₂O as carrier gas, the plateaus of vapor concentrations were lower (Table). When the N₂O solubility phenomenon was eliminated in advance (Figure, d) the immediate vaporizer output was essentially the same as N₂O plateau values (Figure, b). This phenomenon presumably occurred because of different divisions of carrier gas flows inside the vaporizer, depending on the absolute viscosity of the carrier gas. As the carrier gas viscosity decreases, more of it passes through the fixed resistance of the internal bypass of the vaporizer, and less went through the

vaporizing chamber. As Diaz (2) said, "The halothane output is inversely proportional to the absolute viscosity of the carrier gas."

The effects of gas viscosity were also in evidence by the slower rate of initial decrease in vapor concentration with N_2O (Figure, b) and the more rapid increase with O_2 (Figure, c) as carrier gases.

The fluctuations of vapor concentration output found in this study are the consequences of N_2O solubility in the liquid anesthetics plus the effects of the differences in viscosity of the carrier gases passing through vaporizers, which are not designed with a means for compensation for differences in gas viscosity. Stoelting and Nawaf (4) found no significant change in vaporizer output of enflurane (with N_2O as carrier gas at 3 to 8 L/min flows for 10 minutes) from Ohio and Cyprane vaporizers over a range of dial settings from 0.25% to 4.0%. We were unable to duplicate these results (see Table), but instead found a definite decrease in vapor concentration.

When O_2 replaced N_2O as carrier gas (Figure, c) essentially the same quantity of N_2O formerly dissolved into the halothane (Figure, b) escaped into the passing O_2. The areas bounded by these recorded curves and the expected exponential transition curves were approximately equal.

The transient changes in vapor concentrations found in the present study reflected the altered flows of gases out of the vaporizing chamber, with N_2O dissolving into and then leaving solution. With approximately 100 ml of halogenated liquid anesthetic filling vaporizers, saturation and desaturation with N_2O was achieved in 1 minute. With the 6 L/min carrier gas flow used (480 ml/min flow into the halothane vaporizing chamber) the saturation with N_2O of liquid halothane could not have been completed in much less than 1 minute. Lin (1) has shown

that marked depression of vapor concentration occurred for up to 1 hour if the switch of carrier gas from O_2 to N_2O was at very low flows. In that circumstance there was not sufficient N_2O rapidly available to saturate the halogenated liquid anesthetic; N_2O continued to be "trapped" in the liquid and the output of vapor concentration remained decreased.

The performance of flow-over vaporizers can be stable (1) with a maximum constant deviation from the dial setting of vapor concentrations in the plateau range of -10%, provided that the carrier gas composition remains constant. Closed-circuit anesthesia with an out-of-circuit vaporizer presents the problem of changing flow and proportions of O_2 and N_2O passing through the vaporizer. Furthermore, discontinuation of N_2O flow into the closed circuit will cause an increase in vapor concentration released into the circuit. Use of a single gas, such as N_2O, through an out-of-circuit vaporizer, or syringe injections of halogenated anesthetic into the closed circuit are alternatives that would provide a more accurate delivery of anesthetic vapor.

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Plasma Cholinesterase Activity and Tachyphylaxis during Prolonged Succinylcholine Infusion

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DELISLE, S., LEBRUN, M., AND BEVAN, D. R.: Plasma cholinesterase activity and tachyphylaxis during prolonged succinylcholine infusion. Anesth Analg 1982;61:941-4.

Fifteen patients were studied during general anesthesia (nitrous oxide-fentanyl, N = 7 or nitrous oxide-isoflurane, N = 8) to determine the relationship between plasma cholinesterase activity and succinylcholine requirements during prolonged infusion. Using train-of-four stimulation, neuromuscular block was maintained at 90% for at least 1 hour, and plasma cholinesterase was measured at 30-minute intervals. During the infusion, succinylcholine requirements increased in every patient (tachyphylaxis), but there was no significant change in plasma cholinesterase activity. Succinylcholine requirements during the 1st hour of infusion in patients given fentanyl were correlated with preinfusion cholinesterase activity. It is concluded that tachyphylaxis to succinylcholine is not the result of increased metabolism from enzyme induction and that succinylcholine requirement is related to plasma cholinesterase activity.

Key Words: NEUROMUSCULAR RELAXANTS: succinylcholine; ENZYMES: plasma cholinesterase; PHARMACOLOGY: tachyphylaxis.

W HEN LARGE doses of succinylcholine are administered by either repeated bolus injections or continuous infusion, the rate of administration must be increased to maintain a constant level of neuromuscular blockade (1-5). The tachyphylaxis is associated, in time, with the development of a phase II block and these changes in the characteristics of the neuromuscular block occur more rapidly during nitrous oxide-halothane or nitrous oxide-enflurane than nitrous oxide-narcotic anesthesia (6, 7).

Lee (8) proposed that, because the onset of tachyphylaxis and phase II block occurred simultaneously, they were causally related and that tachyphylaxis resulted from self-antagonism between the depolarizing and non-depolarizing effects of succinylcholine. Others have suggested alternative explanations for the tachyphylaxis including a change in receptor sensitivity to succinylcholine or an increase in its rate of metabolism (4). However, serial measurements of plasma cholinesterase concentration have not been made during prolonged exposure to succinylcholine. We measured plasma cholinesterase (PC) concentration before and during succinylcholine infusion administered at a rate adequate to maintain a constant 90% reduction in the force of contraction of the indirectly stimulated adductor pollicis which was measured using train-of-four stimulation. Studies were conducted in patients anesthetized either with nitrous oxide-fentanyl or nitrous oxide-isoflurane.

Methods

The protocol was approved by the Hospital Ethics Committee. After informed consent had been obtained, 15 healthy adult patients, A.S.A. status I or II, with no known or suspected neuromuscular, hepatic, or renal disease, were assigned randomly to receive either nitrous oxide-fentanyl or nitrous oxide-isoflurane anesthesia. Patients in both groups were premedicated with morphine, 0.1 mg/kg, or meperidine, 1 mg/kg, and atropine, 0.4 to 0.6 mg, intramuscularly. Anesthesia was induced with thiopental, 3 to 5 mg/kg, and maintained with 70% nitrous oxide in oxygen. It was supplemented by isoflurane, 1% to 2% (inspired) or fentanyl, 0.25 mg, after induction followed by 0.1 mg every 30 minutes. After intubation, venti-

lation was controlled and the minute volume adjusted to maintain an end-tidal P_{CO_2} of 35 to 40 mm Hg (Hewlett-Packard infrared CO_2 analyzer HP47210A). Blood pressure and electrocardiogram were recorded in all patients. All fluids were administered via a heated waterbath and body temperature remained greater than 35°C.

Neuromuscular transmission was monitored according to the method of Ali et al (9). The ulnar nerve was stimulated supramaximally at the elbow using subcutaneous needle electrodes. Trains-of-four with square pulses of 0.2-msec duration at a frequency of 2 Hz and a train duration of 2 seconds were repeated every 10 seconds using a Grass S48 stimulator and a SIU5 isolation unit. The hand and forearm were immobilized in a splint and the force of adduction of the adductor pollicis was measured with a force-displacement transducer (Grass FT 10) and recorded using a pen-and-ink recorder (Grass polygraph).

After a stable base line had been obtained, a succinylcholine infusion (0.5%) was started using an infusion pump (IMED), at a rate of 10 to 15 mg/min. When the twitch response had disappeared completely, the infusion rate was decreased, and the trachea was intubated. The infusion rate of succinylcholine was then adjusted to keep the first twitch of the train-of-four at 10% to 15% of its preinfusion rate. Infusion rates were calculated for every 10-minute period after the start of the infusion.

Venous blood samples were taken before induction of anesthesia and at 30-minute intervals during succinylcholine infusion. Plasma cholinesterase activity was measured using a spectrophotometric method (10) according to the methods of Kalow and Genest (11), Harris and Whittaker (12), and Whittaker (13). Dibucaine, fluoride, and chloride numbers were also obtained (10). The normal values (± 1 SD) for our laboratory are: plasma cholinesterase activity, 43 to 69 units/L; dibucaine number, 78% to 85%; fluoride number, 57% to 64%; and chloride number, 11% to 20%.

The mean values are presented with the standard error of the mean as the index of dispersion. Probabilities were calculated from Student's t-test for unpaired data where appropriate and the null hypothesis was rejected when $p < 0.05$. Regression lines were constructed by the least-squares regression method.

Results

Both groups of patients were comparable with respect to sex, age, weight, duration of infusion, and total dose of succinylcholine given (Table).

Infusion Rates

After the establishment of a 90% neuromuscular block, the infusion rates necessary to maintain constant blockade increased in all patients. The increase in infusion rate appeared to be greater and to occur more rapidly in patients anesthetized with isoflurane (Fig 1), but there was no significant difference in the mean infusion rates between the two groups at any 10-minute interval.
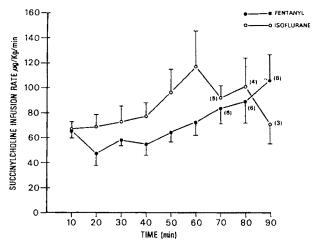
Fig 1. Succinylcholine infusion rates required to maintain 90% block in patients anesthetized with nitrous oxide-fentanyl or nitrous oxide-isoflurane. Means calculated from seven patients in fentanyl group and eight in isoflurane group except where marked (n).

TABLE

Patient Data*

| | Age | Weight | Succinylcholine Infusion | | |
| | | | Duration | Dose | |
				Total	1st hr
	yr	kg	min	mg/kg	
Group 1, fentanyl (two men, five women)	49.4 ± 8.7	63.7 ± 3.6	112.0 ± 12.7	8.5 ± 1.4	3.7 ± 0.4
Group 2, isoflurane (four men, four women)	50.3 ± 4.1	65.3 ± 3.4	107.6 ± 24.4	7.8 ± 1.1	5.0 ± 0.8

* Values are means ± SEM.

Plasma Enzyme Activity

The mean values of PC activity before commencing infusion were within the normal range, and measurements of dibucaine, fluoride, and chloride numbers demonstrated that every patient was homozygous for the normal enzyme. During the infusion there was no significant change in PC activity. There was no evidence of induction of PC activity in any patient and the results were similar during both nitrous oxide-fentanyl and nitrous oxide-isoflurane anesthesia.

Plasma Cholinesterase Activity-Succinylcholine Requirement

There was a linear relationship between preinfusion PC activity and the succinylcholine requirement to maintain constant blockade during the 1st hour of infusion (Fig 2) ($r = 0.8$; $p < 0.05$). Values for patients given isoflurane were not included because patients in this group developed an earlier tachyphylaxis with wide interpatient variation.

Discussion

The use of continuous infusion of succinylcholine in this study has advantages in studying the characteristics of the neuromuscular block produced by long-term succinylcholine infusion. First, by avoiding an initial bolus, the development of train-of-four fade can be seen easily. Second, by maintaining an intense neuromuscular block, 90%, the appearance of phase II block occurs earlier because the depth of neuromuscular block affects the degree of fade (14).

All subjects in the present study developed tachy-

phylaxis and a train-of-four fade of greater than 50% (phase II block) within 1 hour of commencing the succinylcholine infusion. The changing characteristics of the block were associated with no significant change in PC activity. The increasing succinylcholine requirements were thus not the result of increased metabolism brought about by enzyme induction. Therefore, we support Lee and co-workers (3) who suggested that the tachyphylaxis resulted, at least in part, from self-antagonism of the non-depolarizing block by the excitatory effects of succinylcholine. The non-depolarizing blockade may result either from the phase II action of succinylcholine or by the effects of inhalation anesthetics at the neuromuscular junction (15, 16), which would explain the earlier appearance of tachyphylaxis and phase II block with enflurane (7) and isoflurane anesthesia.
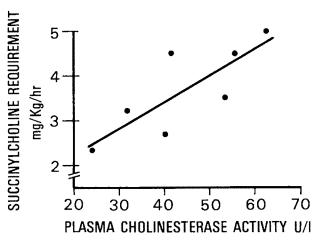
Succinylcholine requirements to maintain 90% neuromuscular block varied between 2.45 to 5.0 mg/kg/hr in the patients anesthetized with nitrous oxide-fentanyl. The drug requirement was correlated significantly with the preinfusion PC activity (Fig 2) despite the small number of patients studied, a finding also reported by Stoddart (17). Some (18, 19), but not all (20), investigations have found correlations between the duration of apnea and PC activity after single bolus doses of succinylcholine. Viby-Mogensen (21) studied 70 genotypically normal patients and found inverse linear relationships between the PC activity and the duration of apnea and the time to 100% recovery of twitch height. However the variation in the duration of apnea was small when PC activity was in the normal range. It is probable that PC activity is more critical for continued metabolism of succinylcholine during prolonged infusion.

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FIG 2. Relationship between preinfusion plasma cholinesterase activity and succinylcholine requirements during 1st hour of infusion.

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CLINICAL reports

Localized Clonic Convulsions after Spinal Anesthesia with Lidocaine and Epinephrine

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The subarachnoid injection of vasoconstrictors to prolong spinal anesthesia has been used since 1903. Transient neurologic complications during and immediately after spinal anesthesia are rare; however, we recently encountered a case of such a complication using lidocaine and epinephrine which warrants comment.

Case Report

A 45-year-old woman, A.S.A. physical status I, was admitted for abdominal hysterectomy for hydatidiform mole. Her past medical history was negative, and she was found to be in good general health. Her pulse rate was 88 beats per minute, blood pressure 120/80 mm Hg, weight 53 kg, and height 160 cm. Skin over the back was normal with no bony deformity of the spine and no neurologic abnormalities in the lower extremities. Hemoglobin was 9.0 g/dl; urinalysis and chest roentgenogram were normal.

Preanesthetic medication with intramuscular meperidine, 50 mg, and promethazine, 25 mg, was given ½ hour before surgery. When wheeled into the operating room, the patient was well sedated. Uneventful lumbar puncture in left lateral position with a 23-gauge needle at the L3-4 interspace was performed with ease, and 1.5 ml of a solution of 5% lido-

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caine in 7.5% dextrose, to which 0.1 ml of epinephrine 1:1000 was added, was slowly injected. The patient was then turned to the supine horizontal position and the legs elevated by 10°. After 5 minutes the level of analgesia to pin prick was at T-6.

The intraoperative period was uneventful. The patient remained sedated with pulse rate between 80 and 100 beats per minute and blood pressure 100 to 120 mm Hg systolic. Hysterectomy with bilateral salpingo-oophorectomy was performed. She received 1500 ml of crystalloid fluids and 300 ml of whole blood intravenously; estimated blood loss was 350 ml. Surgery lasted 1 hour 40 minutes, at the end of which the incision site was still anesthetized and level of pin-prick analgesia was at T-8.

The patient was transferred to the recovery room with intravenous fluids running and legs elevated. After 15 minutes the patient complained of tightness and discomfort at the site of the incision. Analgesia had regressed to T-11 dermatome, and meperidine (25 mg) was given intravenously. Within the next 4 to 5 minutes the patient, still complaining of pain at the site of the incision, suddenly developed bilateral plantar flexion followed by a burst of clonic contractions of the muscles of the abdomen, low back, thighs, and legs, which lasted for approximately 5 seconds. This was associated with severe pain at the site of the incision. The convulsions were limited entirely to the part of the body that had been anesthetized by the spinal anesthesia. The patient remained fully conscious, awake, and well oriented. Subsequent convulsions occurred at intervals of approximately 2 to 3 minutes and lasted 5 to 7 seconds. The patient became apprehensive due to pain and started supporting her abdomen with her hands during the convulsions. Verbal reassurance and oxygenation with 100% oxygen were in vain and, to our surprise, the duration, severity, and frequency of convulsions gradually increased. The pulse rate increased to 130 beats per minute, with a systolic blood pressure of 130 mm Hg, and she started to hyperventilate between convulsions. Intravenous diazepam (10 mg) was then given slowly and within 3 to 4 minutes the convulsions ceased, and the patient went to sleep.

Approximately 15 minutes after the diazepam was given, when the patient was sedated but easily arousable and cooperative, and when we were convinced that the convulsions had been controlled, sensory levels of analgesia and motor power were tested. The level of sensation to pin-prick was L-4 segment with quadriceps femoris function

graded as 4 of 5. The patient was observed closely for the next 24 hours but no further convulsions occurred.

Findings of a complete neurologic examination 48 hours after the anesthetic were normal. The patient remained in the hospital for 1 month for pregnancy tests and prophylactic chemotherapy; reexamination before discharge again showed no neurologic abnormality.

Discussion

Moore et al (1) studied three vasoconstrictors with tetracaine solution for spinal anesthesia in 8851 patients and found that epinephrine, 0.2 mg, safely and consistently prolonged the duration of analgesia by 50%. Park et al (2) also reported a 53% increase in duration and safety using a similar technique. In a double-blind study, Chambers et al (3) compared the duration of spinal anesthesia using plain lidocaine with those when different volumes (0.1, 0.2, 0.3 ml of 1:1000) of epinephrine were added to it. They reported a significant increase in mean time for complete sensory and motor recovery with epinephrine but no significant difference between solutions of different concentrations of epinephrine. These reports and the reports of others on the use of single-dose intrathecal epinephrine with spinal anesthesia confirm that neurologic complications, either transient or permanent, are extremely rare.

Absence of any neurologic abnormality in the present case before or after the anesthetic excludes the possibility of exaggeration of preexisting spinal cord disease by the anesthetic. Trauma to the cauda equina as a cause of the convulsion was unlikely as the muscles involved in the convulsions are innervated from spinal segments as high as T-6. The restriction of the convulsions to the areas denervated by the spinal anesthesia suggest that the convulsions were a manifestation of abnormal spinal cord function associated with the anesthesia, possibly transient hypoxia of the cord due to ischemia.

There is a considerable individual variability in the blood supply to the human spinal cord but almost always the anterior spinal artery, which supplies the anterior two thirds of the cord, has poor collaterals and poor reinforcing anterior radicular arteries. In some individuals only a single large artery, the arteria radicularis magna, may be responsible for most of the blood supply to as much as the distal two thirds of the spinal cord (4). The exact position of this artery varies but it arises from the aorta in the lower thoracic or upper lumbar vertebral levels and approaches the spinal cord along one of the ventral nerve roots.

Transient interruption of blood flow to the spinal cord in man leads to functional as well as structural changes. The vulnerability of the cord to such an insult has been shown by Gilles and Nag (5) to be greater caudally and to involve motor neurons more often than sensory neurons. Zuber et al (6) reported five cases in which anterior spinal artery syndrome developed, resulting in paraparesis or paraplegia following abdominal aortic surgery, due to transient interruption of the blood flow to the spinal cord. They stated that transient damage occurs after 15 minutes and permanent damage after 20 minutes of occlusion, which is aggravated by arterial hypotension.

The classic experiments done in rhesus monkeys by Wu et al (7) help in understanding the clinical picture observed in the present case. In their study, done under thiopental anesthesia, a single subarachnoid injection of 0.3 mg/kg of epinephrine led to hyperextension, rigidity, and tremors of the muscles of the hind limb 2 to 3 minutes following the injection. With 0.6 mg/kg of epinephrine, the effects were more severe and more prolonged and were associated with a vigorous quadriceps response to weak peripheral stimuli with intensification of tremor, indicating a state of hyperalgesia and hyperreflexia. However, the neurologic changes they observed were transient and were followed by complete recovery. They compared their results with those of several other workers who produced acute anoxia of the cord in animals and who observed similar neurologic signs with subsequent histologic preparations showing degeneration of the anterior horn cells. From this Wu et al (7) concluded that the neurologic effects observed in their study with subarachnoid epinephrine were due to hypoxia following reduction in the blood supply to the cord through the vasoconstrictor action of epinephrine. In the case we have presented, we believe that the epinephrine injected with the local anesthetic produced spinal cord ischemia with hypoxic irritability, which was manifested as the anesthesia wore off and somatic motor nerve function returned. However, we cannot rule out the possibility of an anomalous blood supply to the spinal cord (8) as a contributory cause.

A case reported by Fox et al (9) bears some similarity to the one presented here. After spinal anesthesia, a 57-year-old woman who had been given tetracaine and epinephrine developed myoclonus in the lower extremities, and Fox et al attributed this to the action of the local anesthetic drug on the cord itself. Because myoclonus is an extremely rare complication of spinal anesthesia, they did not rule out the possibility of latent spinal cord disease; however, they did

not consider the possibility that epinephrine may have affected spinal cord function. The possible etiology of myoclonus associated with spinal anesthesia is parenthetically discussed by Greene (10). The concentration of local anesthetics in the spinal cord is greater posteriolaterally than anteriorly, and with regression of anesthesia, continued blockade of inhibitory neurons in posteriolateral columns might have persisted beyond the time when anesthetic concentrations in anterior motor columns had decreased below effective concentrations, thus resulting in clonus.

Diazepam in clinical doses has been shown to have a direct effect on the function of human spinal cord (11), including depression of afferent input through the dorsal root within 3 minutes after intravenous administration. Ngai et al (12), however, have shown that in cats the spinal cord is relatively resistant to depression by diazepam, and they suggest that inhibition of polysynaptic cord reflexes is mediated through supraspinal structures, most likely reticular facilitatory system. We found, nevertheless, that in the present case effective suppression of clonic convulsions, which we believe were possibly due to increased spinal cord irritability secondary to cord ischemia, was achieved with approximately 0.2 mg/kg of diazepam given intravenously.

In summary, we present a case in which we hypothesize that epinephrine injected into the subarachnoid space in conjunction with spinal anesthetic caused spinal cord ischemia, with resultant transient and localized seizure activity that was rapidly and effectively controlled with intravenous diazepam.

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Persistent Sixth Cranial Nerve Paresis following Blood Patch for Postdural Puncture Headache

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The incidence of abducens nerve paresis following lumbar puncture has been reported as varying between 1 in 5000 to 1 in 8000 cases (1, 2). It is almost always associated with postlumbar puncture headache (2). The incidence of sixth nerve weakness increases after puncture with large-gauge needles (2), as does the incidence and severity of the accompanying headache (3). Epidural blood patch has been a highly effective mode of treatment (4) for the headache. We present a case of abducens nerve paresis associated with a postdural puncture headache in which the headache was relieved and the nerve weakness persisted.

Case Report

A 34-year-old white woman was admitted in the 35th week of pregnancy because of ruptured membranes. She was not in labor. Two years before admission, a laparotomy had been performed to remove multiple uterine leiomyomata. There were no medical problems and no previous history of headache or diplopia. A cesarean section was planned for the next morning because of the previous surgery and the presence of ruptured membranes. Lumbar epidural anesthesia was explained to the patient.

The patient received sodium citrate, 0.3 M, 30 ml orally, 1 hour before arrival in the operating room. The patient was placed in the sitting position for the initiation of epidural anesthesia at the L2-3 interspace using a 17-gauge Tuohy needle. Cerebrospinal fluid was, however, obtained. The needle was withdrawn and placed in the epidural space at the L3-4 interspace. A catheter was advanced 1 cm into the

epidural space and taped in place. Again, however, clear fluid could be easily aspirated from the catheter in both the sitting and supine positions. With the catheter apparently in the subarachnoid space, it was decided to induce spinal anesthesia. Tetracaine, 12 mg, hyperbaric with glucose 10% was therefore injected in incremental doses. This resulted in anesthesia only of the right leg after 10 minutes. General anesthesia was then administered using thiopental, N_2O-O_2, and a muscle relaxant before delivery of the baby. Apgar score was 9 at 1 and 5 minutes. After extubation, the catheter was removed.

The patient complained of severe fronto-occipito-nuchal headache, which worsened when erect, on the 1st postoperative day. On the 3rd day, dizziness and double vision also developed. Hydration was increased to 4000 ml/day. On the 4th day, 15 ml of autologous blood was injected into the epidural space at the L2-3 interspace. The headache was immediately relieved, but diplopia persisted in both supine and upright positions. Ophthalmologic consultation noted right esotropia in primary gaze. The patient was discharged on the 6th postoperative day with an eye patch for the right eye. The double vision gradually resolved in 6 weeks.

Discussion

Smith (5) attempted to prevent the headache following an inadvertent dural puncture with a large-gauge epidural needle by serial administrations of saline over a 24-hour period through an epidural catheter placed in the epidural space at an interspace different from the puncture site. This reduced the incidence of headache to 7.7% from 64.6%. We initially tried this approach after the "wet tap," but were prevented from following through when it was found that cerebrospinal fluid could be aspirated through the catheter. We thought a second dural hole had been produced and abandoned regional analgesia after our spinal anesthesia using the catheter failed.

Abducens nerve paresis most frequently arises 2 to 5 days following the dural puncture (2). Although the condition usually resolves in 6 to 8 weeks (1), it remains a distressing symptom during this time. Low cerebrospinal fluid pressure is present in both postpuncture headache and sixth nerve weakness, suggesting a common etiology (1, 2). The mechanism of abducens nerve weakness in these cases is thought to involve stretch and resultant injury to this long nerve (2). Low cerebrospinal fluid pressure causes descent of the medulla and pons in the cranial cavity in the upright position. The abducens nerve is then stretched because it is fixed between its origin at the pons and its position in the cavernous sinus. Before the nerve

enters the sinus it passes over the sharp edge of the apex of the petrous portion of the temporal bone. Stretch of a long nerve that is fixed in position may also play a role in injuries of the recurrent laryngeal nerve (6). The current treatment for abducens weakness of this origin is to cover the affected eye with a patch until the diplopia improves. If the diplopia is severe and fails to improve within 6 months, a surgical procedure involving rectus muscle fusion can be considered (7).

On the basis of our experience with this case, we recommend that if significant headache occurs following dural puncture with a large-gauge needle, immediate supine bed rest be instituted to prevent stretch and resultant damage to the sixth nerve, until epidural blood patching can be performed.

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Correlation of Peripheral Venous and Arterial Blood Gas Values during General Anesthesia

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Blood in veins on the back of the hand is derived primarily from cutaneous blood flow that is markedly increased by various inhalation anesthetics (1, 2). France, Eger, and Bendixen (3) have shown that this combination of cutaneous vasodilation and increased blood flow is sufficient to "arterialize" peripheral venous blood during general anesthesia. Their study showed that carbon dioxide partial pressures in peripheral venous blood (Pv_{CO_2}) can be used to assess ventilation adequately during general anesthesia with a variety of agents. (The lower case "v" used throughout this paper represents peripheral venous blood.) However, oxygen partial pressure in peripheral venous blood (Pv_{O_2}) was less reliable as an indicator of arterial oxygenation. The previous work did not evaluate the relationship between venous and arterial Pco_2 [P(a-v)CO_2] and PO_2 [P(a-v)O_2] with regard to specific anesthetics and was performed before the clinical availability of isoflurane.

The purpose of this study was to assess the validity of using peripheral venous blood to evaluate the adequacy of ventilation and oxygenation during clinical anesthesia with isoflurane, enflurane, or halothane. The new agent, isoflurane, is of particular interest because of the marked increase in cutaneous blood flow that occurs with this agent (1).

Methods and Materials

Forty-eight male patients ranging in age from 36 to 72 years were anesthetized with isoflurane (n = 15),

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enflurane (n = 16), or halothane (n = 17) in combination with concentrations of nitrous oxide ranging from 20% to 70% (mean 58%). Paired blood samples were drawn simultaneously from a radial artery and from a cannula placed in a vein on the back of the hand of each patient. All blood samples were drawn during a steady state of ventilation, i.e., 15 minutes after any change in ventilatory rate, tidal volume, or FI_{O_2} during the first hour of anesthesia. All patients were normotensive and none received blood transfusion or vasoactive drugs. This protocol was approved by the University's Committee for the Protection of Human Subjects.

Blood obtained through indwelling catheters was sampled (1.5 ml) after withdrawing a volume equal to at least 6 times (3 ml) the dead space of the catheter in order to prevent hemodilution by flush or intravenous solutions (4). An adequate sample of venous blood could always be obtained without the use of a tourniquet or application of heat to the hand. All blood samples were collected anaerobically in heparinized syringes and analyzed immediately for Pco_2, Po_2, pH, hemoglobin, and calculated base excess by using a Radiometer ABL-1 analyzer. Oxygen content was calculated using the method described by Ruiz et al (5). Comparisons between the anesthetics were accomplished by performing a one-way analysis of variance on each variable. In instances when the analysis of variance was significant, Duncan's multiple range test was performed to determine which of the groups differed. A paired difference t-test was performed to evaluate the difference between the arterial and the venous measurements with each of the three anesthetics. Multiple regression analysis was used to evaluate the correlation between the arterial and the venous measurements.

Results

Arterial Pco_2 was 36.9 ± 11.0 torr (mean ± SD) with a range from 19.8 to 68.6 torr. Arteriovenous Pco_2 differences for each anesthetic are shown in the Table: P(a-v)CO_2 values ranged from −1.2 ± 1.6 torr (mean ± SD) during anesthesia with isoflurane to −1.6 ± 1.6 torr (mean ± SD) with halothane. No significant difference (r = 0.03) was observed between P(a-v)CO_2 values and the inspired nitrous oxide concentrations. Values for Pv_{CO_2} plotted as a function of values for Pa_{CO_2} are shown in Fig 1. Arteriovenous pH differences were 0.01 ± 0.01 during anesthesia with isoflurane and enflurane and 0.02 ± 0.02 with halothane.

TABLE

Differences in Arteriovenous Values during Anesthesia with Three Inhalational Anesthetics*

	Isoflurane (n = 15)	Enflurane (n = 16)	Halothane (n = 17)
P$_{CO_2}$ (torr)	−1.2 ± 1.6	−1.5 ± 2.1	−1.6 ± 1.6
pH	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.02
BE (meq/L)	0.09 ± 0.56†	0.03 ± 0.75†	0.20 ± 0.33
PO$_2$ (torr)	49.5 ± 36.9	39.4 ± 29.1	56.9 ± 52.1
O$_2$ content (vol%)	0.65 ± 0.98	0.57 ± 0.44	0.69 ± 0.46

* Values are means ± SD.
† With these exceptions, all arteriovenous values were significantly different at the 0.05 level.

Mean values for arteriovenous base excess differences ranged from 0.03 meq/L during anesthesia with enflurane to 0.20 meq/L with halothane.

Arterial P$_{O_2}$ was 146.5 ± 61.1 torr (mean ± SD) with a range from 41.2 to 365 torr. Mean P(a-v)O$_2$ values ranged from 39.4 ± 29.1 torr during anesthesia with enflurane to 56.9 ± 52.1 torr with halothane. Corresponding mean arteriovenous oxygen content differences ranged from 0.57 ± 0.44 vol % to 0.69 ± 0.45 vol %. Venous oxygen content (C$_{VO_2}$) values plotted as a function of arterial oxygen content (C$_{aO_2}$) are shown in Fig 2. With the exception of base excess, no significant differences among any of these values were observed that were related to the anesthetic agents.

Discussion

We have shown that, during general anesthesia with isoflurane, halothane, or enflurane in combination with nitrous oxide, values for peripheral venous P$_{CO_2}$, pH, and base excess approximate arterial values closely enough to evaluate the adequacy of ventilation and acid-base status. In contrast to P$_{VCO_2}$ values, P$_{VO_2}$ values were significantly lower than their paired arterial values. Although cutaneous blood flow is increased an average of 5-fold during light levels of isoflurane anesthesia (1), the P(a-v)O$_2$ during isoflurane anesthesia was not significantly different from that observed during either enflurane or halothane anesthesia.

We observed a greater range of values for P(a-v)O$_2$ than were reported by France et al (3). The mean P$_{aO_2}$ in our study was 147 torr and the mean P(a-v)O$_2$ difference was 48.8 torr. The previous study (3) reported a mean P$_{aO_2}$ value of 107 torr and a P(a-v)O$_2$ of only 21 torr. Apparent discrepancies between these P(a-v)O$_2$ values and those we observed, as well as among individual values for our patients, are resolved when oxygen content rather than oxygen partial pressure is considered. This is because arterial admixture
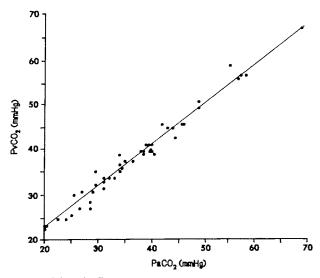
FIG 1. Values for P$_{VCO_2}$ plotted as function of P$_{aCO_2}$ values in 48 patients during anesthesia with either isoflurane, enflurane, or halothane. Regression line is shown; correlation coefficient = 0.99, slope = 0.93, and intercept = 4.08.
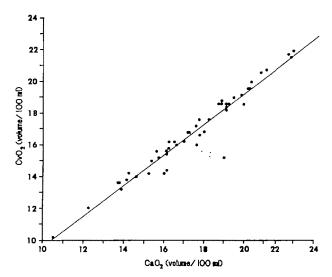
FIG 2. Values for C$_{VO_2}$ are compared with C$_{aO_2}$ values in 48 patients. Regression line is shown; correlation coefficient = 0.95, slope = 0.95, and intercept = −0.17.

is determined not only by the P$_{aO_2}$ but also by the shape of the oxyhemoglobin dissociation curve. Accordingly, in our study, mean values for C(a-v)O$_2$ for the three anesthetics studied ranged from 0.57 to 0.69 vol %.

The relationship between arterial and venous oxygen content is seen in Fig 2. Because the absolute C(a-v)O$_2$ is small, the hemoglobin in venous blood was usually well saturated. Thus, the P$_{VO_2}$ often was sufficiently high to exclude the presence of arterial hypoxemia.

We have found that, during general anesthesia with

isoflurane, enflurane, or halothane, determinations of Pv_{CO_2}, pHv, and calculated venous base excess closely approximated arterial values. Values for Pv_{O_2} were significantly less than for Pa_{O_2} for all three anesthetics but, in approximately 70% of patients, the Pv_{O_2} value was of sufficient magnitude (>70 torr) to discount arterial hypoxemia. This inability to interpret accurately the state of oxygenation from venous blood indicates that an additional analysis of arterial blood still would be required in approximately 30% of patients.

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Unusual Aspects of Low Levels of Pseudocholinesterase in a Pregnant Patient

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Patients with abnormally low levels of pseudocholinesterase or pseudocholinesterase of atypical type (either hetero- or homozygous) may develop prolonged respiratory dysfunction or apnea following the administration of succinylcholine. In these patients such an event usually occurs following the first exposure to this drug. It is generally believed that it is unlikely that a patient will have atypical responses to succinylcholine if he or she in the past has had an uneventful anesthesia that involved use of succinylcholine. In this report, however, we describe a patient who had an uneventful intraoperative and postoperative course following the first exposure to succinylcholine but, during a subsequent procedure, developed prolonged respiratory dysfunction following a second exposure to succinylcholine. This patient was subsequently found to have an extremely low level of pseudocholinesterase.

Case Report

A 28-year-old gravida 2, para 1 with diabetes mellitus was admitted to the hospital at 32 to 34 weeks of gestation because of diabetic ketoacidosis and premature labor. Past medical history included several hospitalizations for control of diabetes mellitus. Four years earlier she was admitted to this hospital during the third trimester of her first pregnancy for management of diabetes mellitus. She subsequently

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underwent an emergency cesarean section for fetal distress under general anesthesia. At that time the anesthesia included pretreatment with metocurine, induction of anesthesia with thiopental, and administration of succinylcholine (150 mg) to facilitate tracheal intubation. Maintenance of anesthesia was with nitrous oxide plus a continuous infusion of succinylcholine (1 mg/min for 10 minutes). The effects of succinylcholine on respiration were not unusual nor was the duration of apnea, and emergence from anesthesia was uneventful.

During the present admission blood pressure was 140/80 torr, pulse rate 80 beats per minute, and the respiratory rate 32 breaths per minute. Uterine contractions were 3 minutes apart, the cervix was 75% effaced and fingertip dilated, with intact membranes. Serum electrolyte levels were normal; blood glucose level was 307 mg/dl. Arterial P_{O_2} was 95 torr, P_{CO_2} 28 torr, and pH level was 7.28. Treatment included morphine, 10 mg IM, for analgesia, intravenous fluids, and a continuous insulin infusion. She received no ester-type local anesthetics for infiltration or paracervical block.

During the next few hours her blood sugar levels decreased following infusion of insulin and glucose. The fetus exhibited tachycardia and late decelerations. As the cervix was only dilated to a fingertip size, fetal scalp blood pH to rule out fetal distress could not be obtained. In view of the fetal distress an emergency cesarean section was planned.

The patient was pretreated with 2 mg of metocurine followed by induction of anesthesia with thiopental followed by succinylcholine (120 mg IV) for tracheal intubation. No additional succinylcholine was administered. Anesthesia was maintained with 0.5% enflurane, nitrous oxide, and oxygen. Following the delivery of the infant, anesthesia was supplemented by incremental doses of fentanyl (total of 150 µg). The operative course was uneventful. When mechanical ventilation was discontinued at the end of the operation (80 minutes following the administration of succinylcholine) the patient had only shallow, rapid respirations. Responses to single and tetanic peripheral nerve stimuli were barely detectable. She responded to verbal commands but could not raise her head and the hand grip was weak. Arterial blood gas tensions, electrolytes, and glucose were all near preoperative levels. Mechanical ventilation was maintained for 5 hours at which time spontaneously generated tidal volume was 500 to 800 ml with a vital capacity of 2500 ml. The patient could also raise her head on command. The tracheal tube was removed. A clinical impression of abnormal pseudocholinesterase or abnormally low levels of pseudocholinesterase associated with pregnancy was considered. Pseudocholinesterase levels and dibucaine and fluoride numbers were measured 11 hours and 3, 9, and 41 days following the operation (Table) (1). Liver function tests showed minimal alterations. On further questioning, the patient denied having taken any medications or having been exposed to organic chemicals.

TABLE

Pseudocholinesterase Levels at Different Times after Delivery

Time of measurement	Pseudocho- linesterase level	Dibucaine no.	Fluoride no.
	units/ml		
11 hr	0.36	47	33
3 days	0.78	58	33
6 days	1.0	Not done	Not done
42 days	4.0	81	61
Normal	7–19	84 ± 3*	49 ± 5*

* Mean ± SE.

She also denied knowledge of any family member who developed similar problems during or after surgery.

Discussion

Prolonged neuromuscular blockade following administration of succinylcholine in a pregnant patient could be due to (a) overdose of drug, (b) potentiation of the drug by the concurrent use of magnesium sulfate or anticholinesterase drugs, (c) the presence of an abnormal pseudocholinesterase, or (d) abnormally low levels of pseudocholinesterase (2–5). Metabolic acidosis or electrolyte abnormalities could also be contributory causes.

The amount of succinylcholine administered (120 mg) in this patient was not considered to be an overdose and she was not receiving magnesium sulfate or anticholinesterase drugs. It has been observed that pseudocholinesterase levels in pregnant patients are significantly lower than in nonpregnant patients (6). Although there have been a few reports of prolonged neuromuscular dysfunction due to low levels of pseudocholinesterase (7), the vast majority of pregnant patients do not develop prolonged respiratory impairment following the administration of the usual amount of succinylcholine. If patients do develop prolonged respiratory dysfunction due to low levels of pseudocholinesterase, it is generally not significant (8). In this patient, 6 hours following the resumption of normal respiratory function, the pseudocholinesterase level was 0.34 units/milliliter (less than 5% of normal values). This is significantly lower than what has been documented in normal pregnant patients (60% normal nonpregnant levels) (6). It has also been observed that in pregnant patients, the lowest level of pseudocholinesterase is measured on the 3rd postpartum day (6, 9). However, in our patient, pseudocholinesterase levels increased to 0.72 units/milliliter on the 3rd postpartum day.

In addition to low level, the pseudocholinesterase in this patient was qualitatively abnormal. Both the dibucaine and fluoride numbers measured in samples of plasma obtained 11 and 72 hours postpartum were abnormal: 47, 58, and 33, 33, respectively. On the basis of these values the patient was initially thought to represent the rare phenotype variant of $E_1^a E_1^f$. However, based on the results of subsequent analyses performed on the 42nd day postpartum, she was considered to have a low level of normal pseudocholinesterase.

There are four aspects of this patient's condition that deserve emphasis. First, the patient did not manifest any respiratory dysfunction on her first exposure to succinylcholine when she had received a larger amount (150 mg) of the drug. Second, she had an abnormally low level of pseudocholinesterase (less than 5% of normal values) associated with pregnancy which apparently had not existed during her earlier pregnancy. Third, the lowest level of pseudocholinesterase was not noted on the 3rd postpartum day. Fourth, dibucaine and fluoride numbers determined in the first few days following delivery were misleading. Viby-Mogensen (8) noted that patients with low levels of normal pseudocholinesterase had prolonged responses to succinylcholine only when the enzyme concentration was less than 15% of normal values. As our patient had a pseudocholinesterase concentration less than 5% of normal value it is possible that this could explain the prolonged respiratory dysfunction produced by succinylcholine. The variability in the pseudocholinesterase concentration that this patient had might have been related to her varying states of diabetes mellitus, dehydration, and general nutrition (9). In addition, during the first pregnancy, she was operated on at 31 weeks of pregnancy at which time the pseudocholinesterase level might have been higher. Although Shnider (6) and Blitt et al (9) noted maximal reduction in the pseudocholinesterase concentration in pregnant patients in the immediate postpartum period (2 to 4 days), earlier investigators (10–12) had observed maximal reduction at other times during pregnancy and labor.

The abnormal dibucaine and fluoride numbers noted in the first and second samples in this patient are puzzling. Perhaps in a pregnant patient with an extremely low level of pseudocholinesterase (less than 1 unit/milliliter or less than 10% of normal values), measurement of dibucaine or fluoride numbers using standard techniques may be misleading. Generally, genotyping and phenotyping of patients with abnormal pseudocholinesterase is done based mainly on

the measurement of dibucaine and fluoride numbers. If we had not measured the dibucaine and fluoride number on the 42nd postpartum day in this patient, then she would have been considered to have an abnormal form of the enzyme. Perhaps this might explain an occurrence in the study of Viby-Mogensen (13): some of the patients who had earlier been found to have abnormal forms of pseudocholinesterase, did not have abnormal responses to usual doses of succinylcholine at a later time.

ACKNOWLEDGMENT

ADDENDUM

Samples of plasma from normal patients (pseudocholinesterase level of approximately 10 units/milliliter) when diluted ten times were found to have values less than the estimated values. The dibucaine and fluoride numbers in those samples were also found to be abnormally low.

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letters TO THE EDITOR

Blood Pressure Measurement in Infants

To the Editor:

We read with interest Friesen and Lichtor's paper (1). Their study concluded that the Dinamap device is an accurate method of monitoring blood pressure in infants. We feel, however, that the conclusions drawn in this paper are inaccurate because inappropriate methods were used to analyze the data.

Each of the comparisons between Dinamap and either a Doppler or arterial line measurement were performed as a linear regression analysis by "lumping" all infants. In fact, the individual regression lines for each infant could be far from identity with a poor correlation coefficient. The composite of these individual lines may create a line that is near identity with a high correlation coefficient, thus creating a deceptive finding.

We have recently performed a similar study comparing Dinamap readings with both umbilical catheter and radial arterial catheter pressures in sick newborns with prolonged continuous readings (manuscript in preparation). In fact our lumped data seemed to show close comparability with methods. However, when we looked at each baby the regression lines were quite disparate.

We wish to call your attention to this error for we do not find that the Dinamap is as accurate a monitor in newborns as we would like it to be.

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To the Editor:

When one collects data for linear regression analysis, there are basically two acceptable ways of going about it. One may collect either a small number of paired determinations from a large number of subjects or a large number of paired determinations from a small number of subjects. Because of the time constraints of our study (we collected data only during anesthesia), we elected to use the former method, whereas Myerberg and Krall have chosen the latter. Both methods are perfectly valid.

We, too, found some individual variation in regression lines, but among our infants, this occurred toward identity as well as away from it. The effect of individual variation has less impact when large numbers of subjects are used.

We also recognize that data from almost any study may not yield identical results when statistically analyzed by different methods. The point is, however, that we used a valid method of data collection and statistical analysis. The results of that analysis justified our conclusions.

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Pulmonary Air Embolism and Nitrous Oxide Challenge

To the Editor:

Shapiro et al (1) presented an interesting concept for detecting residual pulmonary gas following venous air embolism. While in normal circumstances the lungs appear to be complete in their filtration of venous bubbles, at least to diameters as small as 15 to 22 μm (2), spillover of bubbles into the systemic circulation may occur in certain situations, e.g., pharmacologicals (2), volume overload with gas (2, 3) or oxygen toxicity (4). Often when arterial spillover occurs there may be a delay before bubbles are detected, allowing adequate time for size resolution or possible recruitment of surfactants to the air:liquid interface (5), which may facilitate their release. Not all bubbles observed systematically are symptomatic but those injected into the pulmonary veins often appear in the coronary circulation with profound results.

When venous gas is introduced experimentally in dogs at a slow rate, an increase in pulmonary arterial pressure may not be observed until the total volume reaches or exceeds 10 ml. Often this produces a variable increase, below 30% to 40%, in pulmonary arterial pressure. Even after considerable time has elapsed since the initial embolism, a significant amount of residual gas may persist in small pulmonary vessels. In the report of Shapiro et al the Doppler probe appeared not to be positioned so as to detect systemic gas. Although this occurs only rarely, conditions have been reported whereby paradoxical

systemic embolization can occur, even in the absence of arteriovenous shunts. Great care should thus be taken in applying nitrous oxide as a bubble "amplifier" to detect residual pulmonary gas. Pulmonary arterial pressure may not always be the most sensitive indicator of the presence of pulmonary gas, even when observing small changes. Van Liew (6) used nitrous oxide to elicit symptoms in rats that had previously been exposed to decompression and whose lungs presumably contained venous bubbles. He reported a marked increase in mortality following bubble amplification with nitrous oxide.

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book
REVIEWS

In this multiauthored book which originated from a single institution, the contributors have written in a manner so that each chapter could be read separately. Such an approach has resulted in a disjointed structure with a lack of continuity. The intended audience is not made clear. Although the book's purpose is to provide "... a clear understanding of the patho-physiologic derangements produced by the various types of heart disease and a familiarity with the physiologic changes accompanying anesthesia and surgery ...," the thrust of the book is unclear. On the one hand, a great deal of discussion is devoted to the technical aspects of placing invasive monitoring devices and collection of blood products in the manner of a manual. Yet, other sections of the book are detailed and informative as a reference source.

The chapter on monitoring is disappointing. Although there is a great detail on manual technique, one must look elsewhere for discussion of electrocardiography (ECG) and electroencephalography (EEG). The discussion of the basis for arrhythmias is a satisfying one. The chapter on radiology is a laudable attempt to familiarize the anesthesiologist with the information derived from angiography. Unfortunately, this effort is largely pictorial and is not combined with an equally informative discussion of echocardiography and nuclear medicine.

The discussion of postoperative management is informative and should be useful to most trainees. The text is generally well referenced even though some sections lack depth.

In summary, the book has some excellent discussions, contains some deficiencies, and suffers most from a lack of continuity and constant level of intent. I would hesitate to recommend the book as a first or single choice for an individual at the fellowship level although it contains a few well-written sections.

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When this book was first published in 1977, it was destined to become one of the major textbooks of its kind. It has certainly been one of the most widely read textbooks of the last few years. The basic organization of the second edition follows the same logical approach already developed in the first edition. The number of contributors has been increased to a total of 10; all are well-recognized authorities in their respective fields.

Each chapter has a sublist of contents, which helps the reader to prepare his mental attitude before starting to read. Subtitles of each chapter appear at the top of each even-numbered page; the title of the chapter appears at the top of the odd-numbered page. This is a reversal of the arrangement in the first edition and represents careful editing. It is a more logical arrangement and certainly a welcome change. So much for the evolution and style of this second edition.

Most chapters have been revised and updated; very little has been deleted from the first edition. The unique and excellent chapters on "The Respiratory Environment" and "Chest Trauma" need no further comment. The most significant improvement, however, is the addition of chapters on "The Respiratory Pump" and "Disorders of the Respiratory Pump." The former is a concise summary on the respiratory regulatory mechanisms involving the chemoreceptors, central nervous system, and effectors (diaphragms and intercostal muscles). The respiratory pattern and reflexes arising from the lung are also included in this chapter. The introductory statement about the physiology of respiration in sleep appears in the chapter, "Disorders of the Respiratory Pump." In this reviewer's opinion, the sleep state is one of the basic physiologic factors that profoundly affect the respiration and breathing pattern. Therefore, it would have been more appropriately included in the chapter on the respiratory pump. On the other hand, "Abnormalities of the Chest Wall" (chapter 11 in the first edition) is now incorporated into the chapter, "Disorders of the Respiratory Pump." In "Chronic Noninfectious Parenchy-

mal Diseases," hypereosinophilic syndrome and tropical eosinophilia are newly added. The question of angiotensin converting enzyme in sarcoidosis, not mentioned in the first edition, has now been added under immunology and prognosis and therapy. The discussion on aspergillosis is much more detailed. There is a timid attempt to introduce certain aspects of cystic fibrosis here and there in different chapters. Through much improved pulmonary and nutritional therapies, many patients with cystic fibrosis are now outliving the pediatric age limit and they are now adults knocking at the doors of pulmonologists.

For anesthesiologists, there is a valuable section on the effects of general anesthesia in the chapter, "Chest Trauma." Expanded discussions on the effect of positive end-expiratory pressure (PEEP) and continuous positive airway pressure (CPAP) in adult respiratory distress syndrome (ARDS) are a welcome revision to intensivists.

References are carefully chosen and updated, in general, through 1979 to 1980. There has been no deterioration in the quality of figures and roentgenogram reproduction since the first edition.

In summary, the editor and associate editor of this book have succeeded admirably in updating the information, reorganizing the chapters in an appropriate manner, and correcting most of the deficiencies in the first edition. I highly recommend this book to any pulmonologist and to other specialists who require basic knowledge of pulmonology in practicing their particular specialty.

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Clinical Uses of Mechanical Ventilation, edited by C. C. Rattenborg and E. Via-Reque, Chicago, Year Book Medical Publishers, 1981, 363 pp, $16.00.

This book was designed to provide a text embracing all aspects of mechanical ventilation. It is written for physicians and respiratory therapists who are involved in the management of patients requiring mechanical ventilatory support in intensive care units. Some of the text would be useful for medical students in the latter part of training.

The text is divided into five parts: administration of mechanical ventilation, disorders that may require mechanical ventilation, patient management, effects and complications of mechanical ventilation, and nonmedical problems. Each part is then divided into a series of chapters written by different authors. The book appears to have all the characteristics of a completely balanced text on mechanical ventilation. Unfortunately, because of the multiplicity of authors, the chapters—even within a specific section—are without flow.

The opening chapter charges into the mechanics of ventilation without giving the reader an opportunity to settle down with the book. This is followed by an unnecessarily complicated chapter on acid base balance, after which the reader's interest in completing the remainder of the book has rapidly declined.

The clinical section is presented with a clearer style, but I was disappointed to see aspiration pneumonia, which was defined as "the result of major aspiration of gastric contents," included and described in the chapter on infectious diseases. The chapters on Swan-Ganz catheters, which pre-

sumably apply to all flow-directed pulmonary arterial catheters, and radiologic aspects of mechanical ventilation were well-written, useful contributions. A chapter on trauma, and particularly chest trauma, is sadly lacking. Each chapter is concluded with a list of references which range from four to more than 30.

I was disappointed not to find a chapter on the history of mechanical ventilation and the evolution of ventilators over the past 35 years.

The book had the potential of a regal text, but there are many paupers in the kingdom. In spite of this it should be included in intensive care units and hospital libraries. This book should be prescribed reading for fellows, residents, and therapists involved in the clinical use of mechanical ventilation.

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BOOKS RECEIVED

A History of Medicine in Alabama, by H. L. Holley, University, Alabama, The University of Alabama Press, 1982, 418 pp, $35.00.

Medicine for Anaesthetists, edited by M. D. Vickers, with foreword by W. W. Mushin, Oxford, Blackwell Scientific Publications, 1982, 647 pp, $65.00.

Anesthesia Review 1, edited by L. Kaufman, with foreword by M. K. Sykes, New York, Churchill Livingstone Inc., 1982, 148 pp, $24.75.

Recent Advances in Anesthesia and Analgesia—Number Fourteen, by R. Atkinson and C. L. Hewer, New York, Churchill Livingstone Inc., 1982, 182 pp, $24.00.

A Guide for Authors

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Manuscripts

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as described in Annals of Internal Medicine 1979; 90: 95–9, and Lancet 1979; 1: 428–30.

Type manuscripts on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in or 8½ by 11 in) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations.

Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

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Introduction. Clearly state the *purpose* of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

Methods. Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

Results. Present your results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations: emphasize or summarize only important observations.

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The only acceptable references to journal articles or abstracts are those appearing in peer-reviewed journals. Abstracts in peer-reviewed journals are acceptable only if less than 4 years old. List articles accepted for publication but not yet in print as "in press." Three copies of "in press" references must accompany each article submitted for editorial review. Articles submitted but not yet accepted for publication must be cited in the text as "unpublished data" (in parentheses).

References must be verified by the author(s) against the original documents.

Examples of correct forms:

Journal

1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al)

Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687-90.

2. Corporate Author

The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119-25.

Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224-5.

Books and Other Monographs

3. Personal Author(s)

Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

7. Agency Publication

National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

Tables. Type each table on a separate sheet; remember to double space. Do not submit tables as photographs. Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use the following symbols in this sequence: *, †, ‡, §, ‖, ¶, #, **, ††. . . . Identify statistical measures of variation such as SD and SEM.

Omit internal horizontal and vertical rules.

Cite each table in the text in consecutive order.

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Abbreviations. Define all abbreviations except those approved by the International System of Units for amount of substance, mass, length, time, temperature, electric current, and luminous intensity. Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

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Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy: Safe use of chloroprocaine HCl has not been established with respect to adverse effects upon fetal development. This fact should be carefully considered before administering the drug to women of childbearing potential, particularly during early pregnancy.

Obstetrical Paracervical Block: Chloroprocaine is not recommended for obstetrical paracervical block when toxemia of pregnancy is present or when fetal distress or prematurity is anticipated in advance of the block. Fetal bradycardia has been noted by electronic monitoring in about 5-10% of the cases where initial doses of 120 mg to 140 mg of chloroprocaine were used. The incidence of bradycardia, within this dose range, might not be dose related. These data are limited and are generally restricted to non-toxemic cases where fetal distress or prematurity was not anticipated in advance of the block. The role of drug factors and non-drug factors associated with fetal bradycardia following paracervical block are unexplained at this time.

In obstetrics, some oxytocic drugs may cause severe persistent hypertension if vasoconstrictor drugs are used to correct hypotension or are added to the local anesthetic solution.

Solutions containing vasoconstrictors, particularly epinephrine and norepinephrine, should be used with extreme caution in patients receiving MAO inhibitors and tricyclic antidepressants, since severe prolonged hypertension may occur.

Precautions: The safety and effectiveness of chloroprocaine HCl depends upon proper dosage, correct technique, adequate precautions and readiness for emergencies.

Solutions containing vasoconstrictors should be used cautiously in the presence of disease which may adversely affect the patient's cardiovascular system, in areas where the blood supply is limited, or when peripheral vascular disease is present.

Injections should always be made slowly and with frequent aspiration to avoid inadvertent rapid intravascular administration which can produce systemic toxicity.

Serious cardiac arrhythmias may occur if preparations containing a vasopressor are used in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other related agents.

Adverse Reactions: *Systemic adverse reactions result from high plasma levels due to rapid absorption, inadvertent intravascular injection, excessive dosage, hypersensitivity, idiosyncrasy, or diminished tolerance. Central nervous system reactions:* excitation and/or depression; restlessness, anxiety, dizziness, blurred vision, or tremors, possibly proceeding to convulsions. Depression may be the first manifestation followed by drowsiness merging into unconsciousness and respiratory arrest.

Cardiovascular system reactions: depression of the myocardium manifested by an initial episode of hypotension, bradycardia, and cardiac arrest.·

Neurologic adverse reactions: In the practice of epidural block, occasional inadvertent penetration of the subarachnoid space may occur; subsequent reactions may include spinal block of varying magnitude, loss of bowel and bladder control, loss of perineal sensation and sexual function. Persistent neurological deficit of some lower spinal segments with slow recovery (several months) has been reported in rare instances.

Dosage and Administration: See full prescribing information.

NESACAINE is supplied in 1% and 2% solutions in 30 ml multiple dose vials.

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Class of tranquilizer	**Major**	Minor	Minor	Minor
Elimination half-life	**2.3 hrs.**	27-37 hrs.	16 hrs.	3-4 hrs.
Antiemetic activity	**Signifi-cant**	No	No	Mild
Alpha-adrenergic blockade	**YES**	No	No	No
May be used both IM and IV	**YES**	Yes (IM preferred)	Yes	No
Less pain on injection	**YES**	No	No	No
Same syringe compatibility with atropine, scopolamine	**YES**	No	No	Yes

Please see brief summary of Prescribing Information on next page.

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Inapsine®
(droperidol) Injection

Inapsine® (droperidol) Injection ℞

*Before prescribing please consult complete prescribing information, of which the following is a brief summary.

DESCRIPTION:

2 ml. and 5 ml. ampoules
Each ml. contains:
Droperidol...2.5 mg.
Lactic acid for pH adjustment to 3.4 ± 0.4
10 ml. vials
Each ml. contains:
Droperidol...2.5 mg.
With 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY
Droperidol is a neuroleptic (tranquilizer) agent.

INDICATIONS: INAPSINE (droperidol) is indicated:
to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures;
for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia;
in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.
If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.
The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.
If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.
Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.
Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.
When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.
Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.*

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.
Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.
Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).
When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated respiratory arrest could occur. Elevated blood pressure, with or without preexisting hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved. Vital signs should be monitored routinely.
Usual Adult Dosage
I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.
II. Adjunct to General Anesthesia
    Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
    Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
    If INNOVAR® injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.
III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
    Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.
IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

HOW SUPPLIED: 2 ml. and 5 ml. ampoules-packages of 10; 10 ml. multiple-dose vials—packages of 10.
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DESCRIPTION

ETHRANE (enflurane) (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether) (CHF2OCF2CHFCl) is a nonflammable inhalation anesthetic agent. The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation.

$$\log_{10} P = A + B/T \qquad \begin{aligned} A &= 7.967 \\ B &= -1678.4 \\ T &= {}^\circ C + 273.16 \text{ (Kelvin)} \end{aligned}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20°C is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C.

Enflurane is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary even in the presence of ultraviolet light. Enflurane is stable to strong base and does not decompose in contact with soda lime and does not react with aluminum, tin, brass, iron or copper. The partition coefficients of enflurane at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ETHRANE (enflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70 percent nitrous oxide—30 percent oxygen, and 1.17 in 30 percent nitrous oxide—70 percent oxygen.

Induction and recovery from anesthesia with enflurane are rapid. Enflurane has a mild, sweet odor. Enflurane may provide a mild stimulus to salivation or tracheobronchial secretions. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia can be changed rapidly by changing the inspired enflurane concentration. Enflurane reduces ventilation as depth of anesthesia increases. High PaCO2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. Enflurane provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during enflurane anesthesia. Enflurane anesthesia has been used in excision of pheochromocytomas in men without ventricular arrhythmias. On the basis of studies in patients anesthetized with enflurane and injected with epinephrine containing solutions to achieve hemostasis in a highly vascular area (transsphenoidal surgery), it is recommended that 2 micrograms per kilogram (2 μg/kg) of epinephrine may be injected subcutaneously over a 10 minute period. This may be repeated up to 3 times per hour.

Example: Up to 10 ml of 1:100,000 epinephrine containing solution (10 μg/ml) may be injected subcutaneously over a 10 minute period in a 50 kilogram patient judged to have ordinary tolerance to epinephrine administration. No more than 30 ml of 1:100,000 epinephrine containing solution (10 μg/ml) should be administered to such a patient per hour. The concomitant administration of lidocaine enhances the safety of the use of epinephrine during enflurane anesthesia. This effect of lidocaine is dose related. All customary precautions in the use of vasoconstrictor substances should be observed.

Example Two: Alternatively, up to 20 ml of 1:200,000 epinephrine containing solution (5 μg/ml) may be substituted for 10 ml of 1:100,000 solution in the above example.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with enflurane. The NON-DEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of enflurane.

Biotransformation of enflurane in man results in low peak levels of serum fluoride averaging 15 μM/L. These levels are well below the 50 μM/L threshold level which can produce minimal renal damage in normal subjects. However, patients chronically ingesting isoniazid or other hydrazine containing compounds may metabolize greater amounts of enflurane. Although no significant renal dysfunction has been found thus far in such patients, peak serum fluoride levels can exceed 50 μM/L, particularly when anesthesia goes beyond 2 MAC hours. Depression of lymphocyte transformation does not follow prolonged enflurane anesthesia in men in the absence of surgery. Thus enflurane does not depress this aspect of the immune response.

Enflurane 0.25 to 1.0 percent (average 0.5 percent) provides analgesia equal to that produced by 30 to 60 percent (average 40 percent) nitrous oxide for vaginal delivery. With either agent, patients remain awake, cooperative, and oriented. Maternal blood losses are comparable. These clinical approaches produce normal Apgar scores. Serial neurobehavioral testing of the newborn during the first 24 hours of life reveals that neither enflurane nor nitrous oxide analgesia is associated with obvious neurobehavioral alterations. Neither enflurane nor nitrous oxide when used for obstetrical analgesia alters serum BUN, creatinine, uric acid or osmolality. The only difference in the use of these two agents for obstetrical analgesia appears to be higher inspired oxygen concentration that may be used with enflurane.

Analgesic doses of enflurane, up to approximately 1 percent do not significantly depress the rate or force of uterine contraction during labor and delivery. A slowing of the rate of uterine contraction and a diminution of the force of uterine contraction is noted between the administration of 1 and 2 percent delivered enflurane; concentrations somewhere between 2 and 3 percent delivered enflurane may abolish uterine contractions. Enflurane displaces the myometrial response curve to oxytocin so that at lower concentrations of enflurane oxytocin will restore uterine contractions; however, as the dose of enflurane progresses (somewhere between 1.5 and 3 percent delivered enflurane) the response to oxytocin is diminished and then abolished. Uterine bleeding may be increased when enflurane is used in higher concentrations for vaginal delivery or to facilitate delivery by Cesarean section; however, this has not been demonstrated within the recommended dosage range (see DOSAGE AND ADMINISTRATION section). Mean estimated blood loss in patients anesthetized for therapeutic abortion with 1 percent enflurane in 70 percent nitrous oxide with oxygen is approximately twice that noted following therapeutic abortion performed with the use of a local anesthetic technique (40 ml versus 20 ml).

INDICATIONS AND USAGE

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Enflurane may be used to provide analgesia for vaginal delivery. Low concentrations of enflurane (see DOSAGE AND ADMINISTRATION) may also be used to supplement other general anesthetic agents during delivery by Cesarean section. Higher concentrations of enflurane may produce uterine relaxation and an increase in uterine bleeding.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS)
Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics
Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern seen associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentrations usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged enflurane anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to depth of anesthesia. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

PRECAUTIONS

The action of nondepolarizing relaxants is augmented by ETHRANE (enflurane). Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from neuromuscular blockade will be longer in the presence of enflurane than when halothane or nitrous oxide with a balanced technique are used.

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. Enflurane should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug.

In susceptible individuals, enflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc. The syndrome of malignant hyperthermia secondary to enflurane appears to be rare; by March 1980, 35 cases had been reported in North America for an approximate incidence of 1/725,000 enflurane anesthetics.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO2 absorption system (hot canister). PaO2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., enflurane), administration of intravenous dantrolene, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. Renal failure may appear later, and urine flow should be sustained if possible.

Swiss ICR mice were given enflurane to determine whether such exposure might induce neoplasia. Enflurane was given at ¼, ½, and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice who were given the same background gases, but not the anesthetic.

Exposure of mice to 20 hours of 1.2 percent enflurane causes a small (about ¼ of 1%) but statistically significant increase in sperm abnormalities. In contrast to these results, in vivo approaches to the study of mutagenesis (Ames test, sister chromatid exchange test, and the 8-azaguanine system) have not shown a mutagenic effect of enflurane.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to enflurane. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, the drug should be used during pregnancy only if clearly needed

ADVERSE REACTIONS

1. Malignant hyperthermia
2. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia
3. Hypotension and respiratory depression have been reported
4. Arrhythmias, shivering, nausea, and vomiting have been reported
5. Elevation of the white blood count has been observed

OVERDOSAGE

In the event of overdosage, the following action should be taken:
Stop drug administration; establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:
a) vaporizers calibrated specifically for enflurane;
b) vaporizers from which delivered flows can easily and readily be calculated

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by enflurane and that enflurane does not alter heart rate. The use of anticholinergic drugs is a matter of choice.

Surgical Anesthesia: Induction may be achieved using enflurane alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the enflurane mixture. In general, inspired concentrations of 2.0-4.5 percent enflurane produce surgical anesthesia in 7-10 minutes.

Surgical levels of anesthesia may be maintained with 0.5-3 percent enflurane. Maintenance concentrations should not exceed 3 percent. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of enflurane concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Analgesia: Enflurane 0.25 to 1.0 percent produces analgesia for vaginal delivery equal to that produced by 30 to 60 percent nitrous oxide. These concentrations normally do not produce amnesia. See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section.

Cesarean Section: Enflurane should ordinarily be administered in the concentration range of 0.5 to 1.0 percent to supplement other general anesthetics. See also the information on the effects of enflurane on uterine contraction contained in the CLINICAL PHARMACOLOGY section.

HOW SUPPLIED

ETHRANE (enflurane) is packaged in 125 and 250 ml amber-colored bottles.

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*Note: Respiratory depression may last longer than analgesic action and this risk increases with increasing doses.

1. McClain DA and Hug CC, Jr.: Intravenous fentanyl kinetics. *Clin Pharmacol Ther* 28(1): 106-114, 1980.

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RESUSCITATION EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.
See also discussion of narcotic antagonists in Precautions and Overcosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition. Where moderate or high doses are used (above 10 mcg./kg.), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received SUBLIMAZE (fentanyl). It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Drug Dependence—SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure—SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children—The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy—The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS
The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of SUBLIMAZE (fentanyl) are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol) hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol).

When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS
As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (cystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with *INAPSINE* (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION
50 mcg. = .05 mg. = 1 ml.

Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

I. *Premedication*—Premedication (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered *intramuscularly* 30 to 60 minutes prior to surgery.

II. *Adjunct to General Anesthesia*—See Dosage Range Chart

III. *Adjunct to Regional Anesthesia*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

IV. *Postoperatively (recovery room)*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usual Children's Dosage: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 20 to 30 mcg. (0.02 to 0.03 mg.)(0.4 to 0.6 ml.) per 20 to 25 pounds is recommended.

DOSAGE RANGE CHART

TOTAL DOSAGE
Low dose—2 mcg./kg. (.002 mg./kg.) (.04 ml./kg.) SUBLIMAZE* injection. Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period. *Maintenance:* Additional dosages of SUBLIMAZE* injection are infrequently needed in these minor procedures.

Moderate dose—2-20 mcg./kg. (.002-.02 mg./kg.)(.04-0.4 ml./kg.) SUBLIMAZE* injection. Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential. *Maintenance:* 25 to 100 mcg. (0.025 to 0.1 mg.)(0.5 to 2.0 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

High dose—20-50 mcg./kg. (.02-.05 mg./kg.)(0.4-1 ml./kg.) SUBLIMAZE* injection. During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20-50 mcg./kg. (.02-.05 mg.)(0.4-1 ml.) of SUBLIMAZE* injection with nitrous oxide oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH, and prolactin.

When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression.

The main objective of this technique would be to produce "stress free" anesthesia. *Maintenance:* Maintenance dosage (ranging from 25 mcg. (.025 mg.)(0.5 ml.) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

As a General Anesthetic
When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg./kg. (.05 to 0.1 mg./kg.)(1 to 2 ml./kg.) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg./kg. (.15 mg./kg.)(3 ml./kg.) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

OVERDOSAGE
Manifestations: The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; and oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

HOW SUPPLIED
2 ml. and 5 ml. ampoules—packages of 10.
NDC 50458-030-02 NDC 50458-030-05

10 ml. and 20 ml. ampoules—packages of 5.
NDC 50458-030-10 NDC 50458-030-20
(For intravenous use by hospital personnel specifically trained in the use of narcotic analgesics).

March, 1980. Revised June, 1980. January, 1981
U.S. Patent No. 3, 164 600

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JPI-255

Ketalar®

(Ketamine Hydrochloride Injection, USP)

Before prescribing, please see full prescribing information. A Brief Summary follows.

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12 PERCENT OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT DREAM-LIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY IS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY AND THE INCIDENCE IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

THE INCIDENCE OF PSYCHOLOGICAL MANIFESTATIONS DURING EMERGENCE, PARTICULARLY DREAM-LIKE OBSERVATIONS AND EMERGENCE DELIRIUM, MAY BE REDUCED BY USING LOWER RECOMMENDED DOSAGES OF KETALAR IN CONJUNCTION WITH INTRAVENOUS DIAZEPAM DURING INDUCTION AND MAINTENANCE OF ANESTHESIA. (See Dosage and Administration.) ALSO, THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS.

IN ORDER TO TERMINATE A SEVERE EMERGENCE REACTION THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRASHORT-ACTING BARBITURATE MAY BE REQUIRED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS. THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

INDICATIONS AND USAGE

Ketalar is indicated as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best suited for short procedures but it can be used, with additional doses, for longer procedures.

Ketalar is indicated for the induction of anesthesia prior to the administration of other general anesthetic agents.

Ketalar is indicated to supplement low-potency agents, such as nitrous oxide.

Specific areas of application are described in the Clinical Pharmacology section.

CONTRAINDICATIONS

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and in those who have shown hypersensitivity to the drug.

WARNINGS

Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

Postoperative confusional states may occur during the recovery period (see Special Note.)

Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

PRECAUTIONS

General

Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.

Because pharyngeal and laryngeal reflexes are usually active, Ketalar should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances. Resuscitative equipment should be ready for use.

The incidence of emergence reactions may be reduced if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).

The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.

In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.

Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

Information for Patients

As appropriate, especially in cases where early discharge is possible, the duration of Ketalar and other drugs employed during the conduct of anesthesia should be considered. The patients should be cautioned that driving an automobile, operating hazardous machinery or engaging in hazardous activities should not be undertaken for 24 hours or more (depending upon the dosage of Ketalar and consideration of other drugs employed) after anesthesia.

Drug Interactions

Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar. Ketalar is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

Usage in Pregnancy

Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended (see Animal Reproduction).

ADVERSE REACTIONS

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of Ketalar alone. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar. Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketalar administration.

It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see Dosage and Administration).

Gastrointestinal: Anorexia, nausea and vomiting have been observed; however, this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see Dosage and Administration).

General: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

OVERDOSAGE

Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

DOSAGE AND ADMINISTRATION

Note: Barbiturates and Ketalar, being chemically incompatible because of precipitate formation, should not be injected from the same syringe.

If the Ketalar dose is augmented with diazepam, the two drugs must be given separately. Do not mix Ketalar and diazepam in syringe or infusion flask. For additional information on the use of diazepam, refer to the Warnings and Dosage and Administration Sections of the diazepam insert.

Preoperative Preparations:

1. While vomiting has been reported following Ketalar administration, some airway protection may be afforded because of active laryngeal-pharyngeal reflexes. However, since aspiration may occur with Ketalar and since protective reflexes may also be diminished by supplementary anesthetics and muscle relaxants, the possibility of aspiration must be considered. Ketalar is recommended for use in the patient whose stomach is not empty when, in the judgment of the practitioner, the benefits of the drug outweigh the possible risks.

2. Atropine, scopolamine, or another drying agent should be given at an appropriate interval prior to induction.

Onset and Duration:

Because of rapid induction following the initial intravenous injection, the patient should be in a supported position during administration.

The onset of action of Ketalar is rapid; an intravenous dose of 2 mg/kg (1 mg/lb) of body weight usually produces surgical anesthesia within 30 seconds after injection, with the anesthetic effect usually lasting five to ten minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anesthesia without producing significant cumulative effects.

Intramuscular doses, from experience primarily in children, in a range of 9 to 13 mg/kg (4 to 6 mg/lb) usually produce surgical anesthesia within 3 to 4 minutes following injection, with the anesthetic effect usually lasting 12 to 25 minutes.

Dosage:

As with other general anesthetic agents, the individual response to Ketalar is somewhat varied depending on the dose, route of administration, and age of patient, so that dosage recommendation cannot be absolutely fixed. The drug should be titrated against the patient's requirements.

Induction:

Intravenous Route: The initial dose of Ketalar administered intravenously may range from 1 mg/kg to 4.5 mg/kg (0.5 to 2 mg/lb). The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg (1 mg/lb).

Alternatively, in adult patients an induction dose of 1.0 mg to 2.0 mg/kg intravenous ketamine at a rate of 0.5 mg/kg/min may be used for induction of anesthesia. In addition, diazepam in 2 mg to 5 mg doses, administered in a separate syringe over 60 seconds, may be used. In most cases, 15.0 mg of intravenous diazepam

or less will suffice. The incidence of psychological manifestations during emergence, particularly dream-like observations and emergence delirium, may be reduced by this induction dosage program.

Note: The 100 mg/ml concentration of Ketalar should not be injected intravenously without proper dilution. It is recommended the drug be diluted with an equal volume of either Sterile Water for Injection, USP, Normal Saline, or 5% Dextrose in Water.

Rate of Administration: It is recommended that Ketalar be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Intramuscular Route: The initial dose of Ketalar administered intramuscularly may range from 6.5 to 13 mg/kg (3 to 6 mg/lb). A dose of 10 mg/kg (5 mg/lb) will usually produce 12 to 25 minutes of surgical anesthesia.

Maintenance of Anesthesia:

The maintenance dose should be adjusted according to the patient's anesthetic needs and whether an additional anesthetic agent is employed.

Increments of one-half to the full induction dose may be repeated as needed for maintenance of anesthesia. However, it should be noted that purposeless and tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic.

It should be recognized that the larger the total dose of Ketalar administered, the longer will be the time to complete recovery.

Adult patients induced with Ketalar augmented with intravenous diazepam may be maintained on Ketalar given by slow microdrip infusion technique at a dose of 0.1 to 0.5 mg/minute, augmented with diazepam 2 to 5 mg administered intravenously as needed. In many cases 20 mg or less of intravenous diazepam total for combined induction and maintenance will suffice. However, slightly more diazepam may be required depending on the nature and duration of the operation, physical status of the patient, and other factors. The incidence of psychological manifestations during emergence, particularly dream-like observations and emergence delirium, may be reduced by this maintenance dosage program.

Dilution: To prepare a dilute solution containing 1 mg of ketamine per ml, aseptically transfer 10 ml (50 mg per ml Steri-Vial) or 5 ml (100 mg per ml Steri-Vial) to 500 ml of 5% Dextrose Injection, USP or Sodium Chloride (0.9%) Injection, USP (Normal Saline) and mix well. The resultant solution will contain 1 mg of ketamine per ml. The fluid requirements of the patient and duration of anesthesia must be considered when selecting the appropriate dilution of Ketalar. If fluid restriction is required, Ketalar can be added to a 250 ml infusion as described above to provide a Ketalar concentration of 2 mg/ml.

Ketalar Steri-Vials, 10 mg/ml are not recommended for dilution.

Supplementary Agents:

Ketalar is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

The regimen of a reduced dose of Ketalar supplemented with diazepam can be used to produce balanced anesthesia by combination with other agents such as nitrous oxide and oxygen.
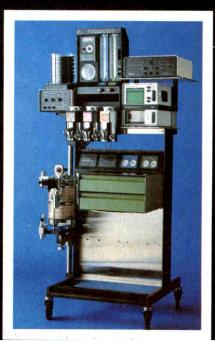
HOW SUPPLIED

Ketalar is supplied as the hydrochloride in concentrations equivalent to ketamine base.

N 0071-4581-15—Each 50-ml vial contains 10 mg/ml. Supplied in cartons of 10.
N 0071-4581-13—Each 25-ml vial contains 10 mg/ml. Supplied in cartons of 10.
N 0071-4581-12—Each 20-ml vial contains 10 mg/ml. Supplied in cartons of 10.
N 0071-4582-10—Each 10-ml vial contains 50 mg/ml. Supplied in cartons of 10.
N 0071-4585-08—Each 5-ml vial contains 100 mg/ml. Supplied in cartons of 10.
4581G030

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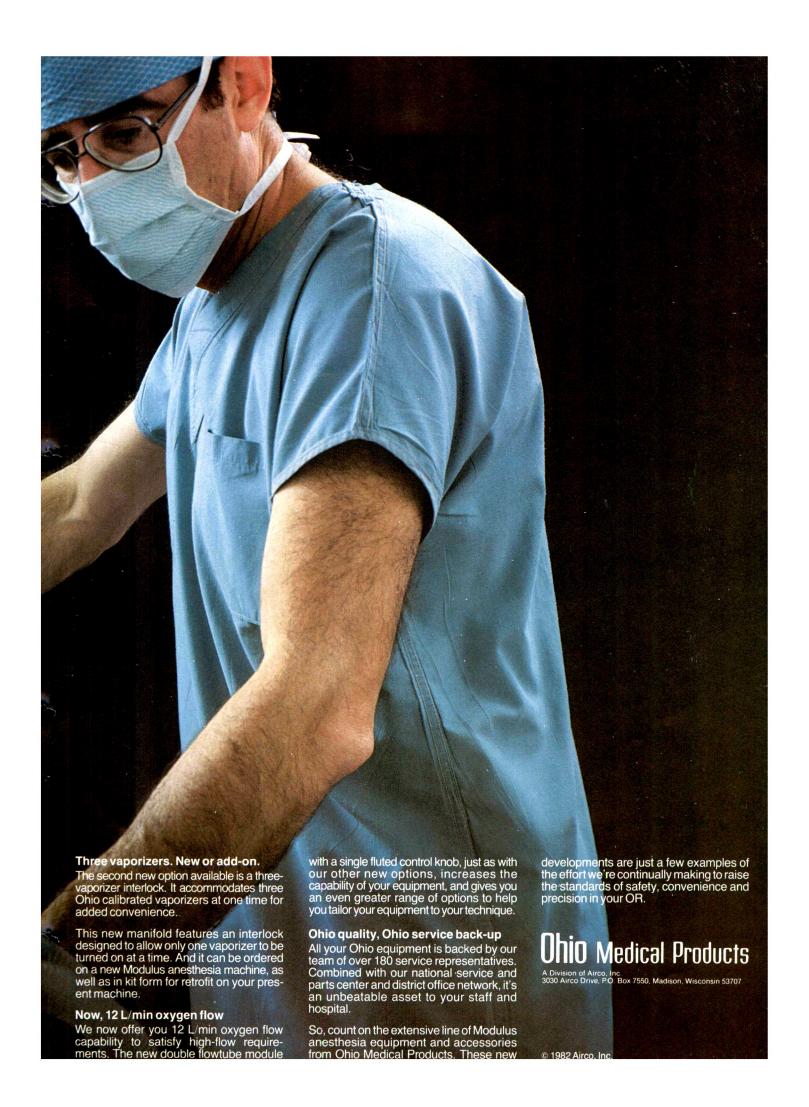
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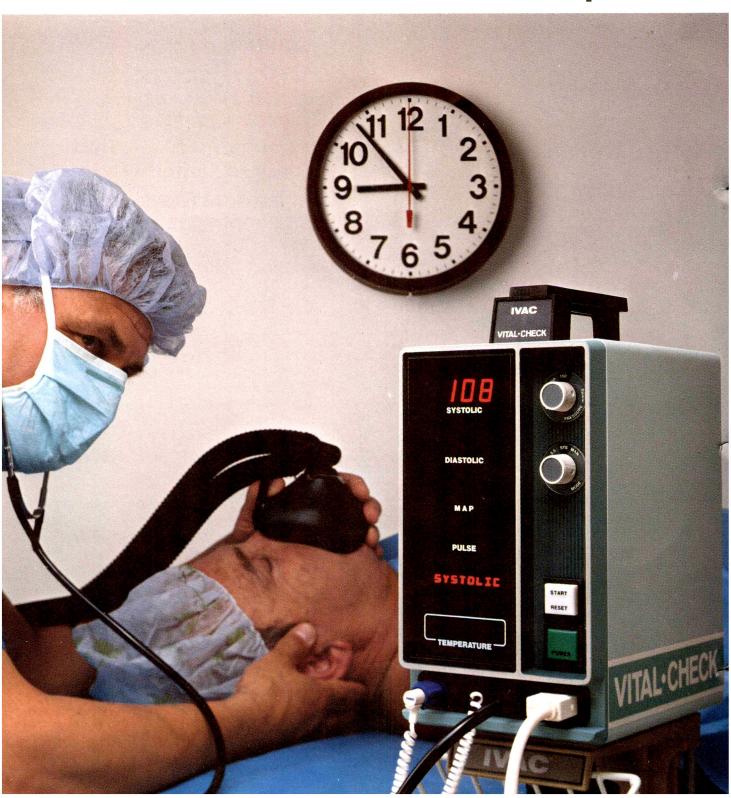
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20 Second
Hands-free continuous update

When patients
would rather
not remember...

ATIVAN® (LORAZEPAM) Ⓥ
INJECTION IM or IV

DESCRIPTION: Ativan® (lorazepam) Injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzo-diazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where patients received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal failure. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately postinjection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure.* Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure.* EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan® (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.

4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.

For IM or IV injection.

Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

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INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
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The International Anesthesia Research Society is pleased to announce the establishment of the **"I.A.R.S. RESEARCH AWARD"**.

Applications for up to $25,000 are invited for the initial Award, to be made in 1983, subject to the following basic conditions:

- ....**The research proposal must be within the general field of anesthesiology.**

- ....**The principal investigator must be a member of the International Anesthesia Research Society.**

- ....**Preference will be given to new investigators.**

- ....**Applications must be received in the I.A.R.S. Cleveland office no later than December 31, 1982.**

The Award will be announced at the Annual Meeting (57th Congress) of the International Anesthesia Research Society to be held in New Orleans, March 13–17, 1983. The Award will be made on July 1, 1983.

The official application form for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

> B. B. Sankey, M.D.
> Executive Secretary
> International Anesthesia Research Society
> 3645 Warrensville Center Rd.
> Cleveland, Ohio 44122, U.S.A.
>
> Telephone: (216) 295-1124

I.A.R.S. 57th Congress — March 13–17, 1983

New Orleans Hilton Hotel

MEETING INFORMATION

SCHEDULE: Sunday, March 13th, 1983
Registration: 2–7 p.m.
Exhibits: 5–7 p.m.
Complimentary Informal Reception: 6–7 p.m.

NOTE: Registration will continue daily throughout the meeting.
Exhibits will continue through Wednesday, noon, March 16th.

SCIENTIFIC PROGRAM: 8 a.m. to 5 p.m. Monday, March 14 through Wednesday, March 16
8 a.m. to 12 noon on Thursday, March 17th.

. . . . 78 Scientific Papers
. . . . 16 Review Course Lectures
. . . . Scientific Exhibits
. . . . Ten "Theme" Luncheons
. . . . The First T.H. SELDON DISTINGUISHED LECTURE to be given by H.J.C. Swan, M.D.—
"The Past and Future in Managing the Cardiovascular System"

PRE-REGISTRATION MATERIAL, HOTEL CARD, DAILY PROGRAM:

Complete meeting information will be mailed by mid-December to all I.A.R.S. members, associate members and educational members.

Non-I.A.R.S. members may receive material by writing or calling the Cleveland business office, 3645 Warrensville Center Rd., Cleveland, Ohio 44122. (216) 295-1124.

REGISTRATION FEES:

	Paid by March 7	*Paid at Meeting*
IARS Members and Associate Members	$115	$125
IARS Educational Members	NO FEE	NO FEE
* New IARS Members and Associate Members	$160	$170
** New IARS Educational Members	NO FEE	NO FEE
Non Members	$175	$185
*** Non Members (residents, nurse trainees)	$ 25	$ 25

* — With membership application, includes dues for one year. (Foreign members add $16.50)
** — With membership application and payment of applicable dues
*** — With letter from program director

CONTINUING EDUCATION CREDITS:

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American Association of Nurse Anesthetists: Prior approval pending for 25 AANA credits.

A Comparative in Vivo Study of Local Neurotoxicity of Lidocaine, Bupivacaine, 2-Chloroprocaine, and a Mixture of 2-Chloroprocaine and Bupivacaine

J. Barsa, MD, FFARCS, M. Batra, MD, B. R. Fink, MD, FFARCS, and S. M. Sumi, MD

BARSA, J., BATRA, M., FINK, B. R., AND SUMI, S. M.: A comparative in vivo study of local neurotoxicity of lidocaine, bupivacaine, 2-chloroprocaine, and a mixture of 2-chloroprocaine and bupivacaine. Anesth Analg 1982;61:961-7.

This study was undertaken because of several recent reports of adverse neurologic reactions following the use of 2-chloroprocaine. Carotid sheaths containing undisturbed vagus nerve were surgically exposed in rabbits and bathed in situ for up to 1 hour in one of the following isotonic solutions: physiologic salt solution, lidocaine 2%, bupivacaine 0.75%, 2-chloroprocaine 3%, or a mixture of 2-chloroprocaine 1.5% and bupivacaine 0.375%. Each solution contained epinephrine, 5 µg/ml, (1:200,000). In other animals the carotid sheaths were bathed in physiologic salt solution, or 2-chloroprocaine 3% without epinephrine. The nerves were excised 10 to 12 days later. C-fiber impulse conduction was normal in nerves that had been exposed to physiologic salt solution with or without epinephrine, to lidocaine, or to bupivacaine. Conduction was absent or markedly impaired in several nerve specimens following exposure to 2-chloroprocaine. Histologic sections revealed the presence of epineurial cellular infiltration and fibrosis, perineurial fibrosis, and axonal degeneration in nerves that had been exposed to 2-chloroprocaine or the mixture of 2-chloroprocaine and bupivacaine. Histologic abnormalities were minor or absent following exposure to lidocaine, to bupivacaine, or to physiologic salt solution. These findings suggest that, under the conditions of the experiments, 2-chloroprocaine is more neurotoxic than lidocaine or bupivacaine.

Key Words: ANESTHETICS, Local: neurotoxicity; TOXICITY: local anesthetics.

NEUROLOGIC complications following regional anesthetic procedures are relatively infrequent (1–5) and usually attributed to faults in technique (5–8). Recently, several adverse neurologic reactions have been reported following inadvertent subarachnoid continuous caudal or epidural anesthesia with 2-chloroprocaine (Nesacaine-CE) (9–11) alone or mixed with bupivacaine. Previous studies of the neural histotoxicity of 2-chloroprocaine and other local anesthetics have been scarce and have not used equipotent doses of different drugs (12–14). In this study, the tissue toxicity of equivalent clinical concentrations of similar volumes of lidocaine, bupivacaine, 2-chloroprocaine,

and bupivacaine-chloroprocaine mixtures were compared in an experimental animal model.

Methods

Animal Preparation

Forty-six 2.5- to 3-kg White New Zealand rabbits were anesthetized with halothane in oxygen, restrained in the supine position. Body temperature was maintained at 38 ± 1°C by a radiant heat lamp and a blanket. Under sterile conditions, an 8- to 10-cm midline incision was made in the skin of the neck. The superficial cervical fascia was incised and the carotid sheath exposed on either side by blunt separation of the sternomastoid and sternohyoid muscles. The muscles were retracted with nylon traction sutures attached to an overlying metal frame to form a trough bounded medially by the trachea and laterally by the sternomastoid muscles. This exposed the carotid sheath (containing the vagus nerve) which remained untouched at the bottom of the trough. The trough was filled with enough solution (2 to 3 ml) to

submerge the carotid sheath completely. Photographs were taken at each stage of the procedure.

The solution was either a physiologic salt solution (GIBCO Medium 199) (Grand Island Biological Company, Long Island, NY) or a fresh (before expiration date) commercial solution of local anesthetic (Lidocaine (Xylocaine) made by Astra, bupivacaine (Marcaine) made by Breon, and 2-chloroprocaine (Nesacaine-CE) made by Pennwalt) or in the case of group 5, a freshly prepared mixture (Table 1). Epinephrine (5 μg/ml) was added to all solutions except group 1B (Medium 199) and group 4B (2-chloroprocaine). Because the acidity of commercial 2-chloroprocaine solution has been suspected as a cause of nerve damage, four of the nerves in group 4A and three of the nerves in group 4B were exposed to the acidic 2-chloroprocaine solution; the others in these groups were exposed to a solution neutralized with sodium bicarbonate to pH 6.8 to 7.2. Solution in the trough was replenished every 10 to 15 minutes to ensure complete submersion of the carotid sheath, an average volume of 7.8 ± 1.2 ml being required; the carotid sheath remained submerged for 45 to 55 minutes, after which the skin incision was closed with metal clips. Following recovery from general anesthesia, the animal was returned to its cage. Ten to 12 days later the rabbit was anesthetized with halothane, the carotid sheath was reexposed and photographed, and the gross appearance noted. The carotid sheath was then incised and the vagus nerve removed.

Impulse Conduction Test

The excised specimen containing the nerve was placed on platinum wire electrodes. The C-fiber component of the compound action potential was elicited by supramaximal 75-V, 0.1-msec stimuli from a Grass S44 stimulator and isolation unit and displayed on a Tektronix-532 cathode ray oscilloscope and recorded on Polaroid film. Nerve conduction was considered

TABLE 1

Treatment Groups

Group	No. of nerves	Epineph-rine (5 μg/ml)
1A—control (medium 199)	9	Yes
1B—control (medium 199)	7	No
2—lidocaine 2%	6	Yes
3—bupivacaine 0.75%	6	Yes
4A—2-chloroprocaine 3%	8	Yes
4B—2-chloroprocaine 3%	6	No
5—chloroprocaine 1.5% and bupivacaine 0.375%	4	Yes

normal if the amplitude of the compound action potential of the experimental nerve was 50% or more of that of its contralateral control, impaired if it was less than 50%. The investigator who measured the compound action potential did not know to which solution the nerve had been exposed.

Histologic Study

Three to four tissue samples were collected from the proximal, middle, and distal parts of each nerve. The samples were fixed in 0.25% glutaraldehyde plus 4% paraformaldehyde and 0.13 M sodium phosphate solution (pH 7.2), postfixed in buffered osmium tetroxide, and embedded in Epon. Transverse sections 0.5- to 2-μ thick were stained with methylene blue or azure blue II for light microscopy. The person who examined the sections was unaware of the treatment to which the source animal had been subjected. The morphologic appearances of the external surrounding tissues, epineurium, perineurium, and axons in each section were studied. Nine to 11 sections from each nerve were scored for evidence of abnormalities or damage in three zones: (a) epineurium (epineurial cellular infiltration, fibrosis), (b) perineurium (perineurial fibrosis), and (c) axon (axonal degeneration). These "zone" scores were averaged to obtain a single value for each zone of each nerve. The scoring was on a scale of 0 to 4, where 0 = no abnormalities, 1 = questionable abnormalities that could be due to artifact, 2 = definite abnormalities involving less than 25% of a cross section of the nerve, 3 = abnormalities involving 25% to 75% of the nerve, and 4 = maximum abnormalities throughout a zone.

Data Analysis

A square root transformation of the average damage scores for each region was performed to stabilize the variance. Two-way analysis of variance of the transformed damage scores using epinephrine (no/yes) and pH (acidic/neutral) as independent variables was performed. No pH-related effect was found in any layer ($p > 0.5$), and so the data from nerves treated with acidic or neutral chloroprocaine solution were pooled for the remainder of the analysis. The square root scores in each treatment group were compared with control scores (physiologic solution Medium 199) and to each other by one-way analysis of variance with linear contrasts (SPSS for DECsystem-10, Version H, Release 9.0, 1981). A probability of less than 0.01 was considered statistically significant as each set of scores was challenged by six comparisons. Two-way analysis of variance was performed on the dam-
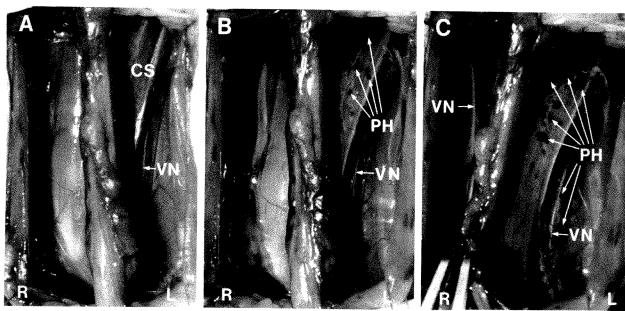
FIG 1. Rabbit cervical preparation showing right (R) and left (L) trough and carotid sheath (CS): A, 1 minute, B, 4 minutes, C, 12 minutes after left trough was filled with 2-chloroprocaine, 3 g/dl (Nesacaine-CE); right trough contained isotonic saline with so-dium bisulphite, 0.2 g/dl, antioxidant in Nesacaine-CE. Note pinpoint hemorrhages (PH) that have developed near left carotid sheath and vagus nerve (VN) in B, and spread distally in C.

TABLE 2

Observations on Nerve Specimens Removed 10 to 12 Days after Exposure to Control and Local Anesthetic Solutions Containing Epinephrine, 5 μg/ml (1:200,000)

Group	Average damage scores (0–4)*			No. of nerves	Pinpoint hemorrhage	Normal action potential
	Epineurial	Perineurial	Axonal			
1A—control	0.18 ± 0.05	0.22 ± 0.04	0.19 ± 0.07	9	0/9	9/9
2—lidocaine 2%	0.16 ± 0.09	0.27 ± 0.04	0.26 ± 0.05	6	0/6	6/6
3—bupivacaine 0.75%	0.27 ± 0.11	0.59 ± 0.13	0.23 ± 0.12	6	0/6	6/6
4A—2-chloroprocaine 3%	2.63 ± 0.20	2.35 ± 0.14	2.16 ± 0.30	8	8/8†	3/8†
5—mixture‡	1.76 ± 0.27	1.98 ± 0.20	2.55 ± 0.30	4	4/4	1/4

* Values are means ± SEM.
† Differs from control ($p < 0.01$) by Fisher's exact test.
‡ Chloroprocaine 1.5% and bupivacaine 0.375%.

age scores using the treatment groups (control versus 2-chloroprocaine) and epinephrine (present versus absent) as independent variables to define the influence of epinephrine on the outcome and to test the significance of an interaction term.

The significance of the associations between the presence of pinpoint hemorrhages (yes/no) versus treatment group, and association of nerve conduction (normal/impaired) versus treatment group was tested by Fisher's exact chi-square test of association.

Results

In Vivo Observations

During exposure to solutions that contained 2-chloroprocaine, pinpoint petechia-like hemorrhages con-sistently developed in tissues surrounding all the nerves (Fig 1 and Table 2). The "petechiae" started to appear a few minutes after the application of solution and increased in size during the exposure. They occurred whether or not the 2-chloroprocaine solution also contained bupivacaine or epinephrine, and whether or not the acidity of the chloroprocaine solution (pH 3.3) was neutralized with sodium bicarbonate to pH 6.8 to 7.2.

No pinpoint hemorrhages were observed in any of the experiments with solutions that did not contain chloroprocaine.

Compound Action Potential

Conduction of electrical impulses appeared normal (compound action potential amplitude exceeded 80%

of control values) in all nerves exposed to control solution with or without epinephrine or to lidocaine or bupivacaine with epinephrine. In contrast, conduction was normal (50% to 100% of control values) in only three of eight nerves exposed to 2-chloroprocaine and epinephrine (conduction was absent in four and impaired in one), and in only one of four nerves exposed to the mixture of 2-chloroprocaine, bupivacaine, and epinephrine (conduction was absent in two and impaired in one). In six nerves exposed to 2-chloroprocaine without epinephrine conduction was normal in four nerves, absent in one, and impaired in one.

Histologic Observations
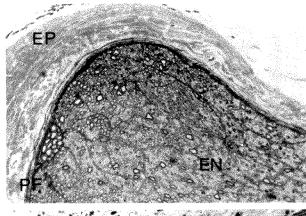
The gross appearance of nerves previously exposed to lidocaine, bupivacaine, and control Medium 199 was similar. Dissection of the nerve was easy, and neural swelling, fibrosis, and adhesions were minimal or absent. In contrast, there was moderate to marked adhesions and fibrosis and the nerve appeared swollen in 15 of 18 nerves exposed to 2-chloroprocaine.
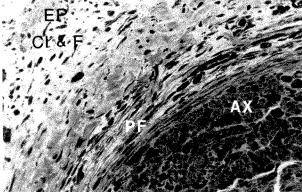
Light microscopic examination (Table 2, Figs 2 to 4) revealed little histologic abnormality in nerves exposed to control solution, to lidocaine, or to bupivacaine (groups 1A, 1B, 2, 3; solutions 1A, 2, and 3 contained epinephrine). In contrast, several nerves exposed to 2-chloroprocaine and the mixture of 2-chloroprocaine and bupivacaine (groups 4B and 5, in which the solutions also contained epinephrine) showed extensive cellular infiltration and thickening of the epineurium involving the entire circumference of the nerve, extensive and marked perineurial fibrosis, and marked axonal degeneration (Table 2, Figs 2 to 4).

Group 4A, exposed to 2-chloroprocaine without epinephrine, showed less histologic abnormality than group 4B, exposed to 2-chloroprocaine and epinephrine (Fig 4).

Damage was noted most frequently when 2-chloroprocaine had been combined with epinephrine (Table 2 and Fig 4). Damage scores and the results of one-way analysis of variance are presented in Table 2 and Fig 3. Damage to all three zones of the nerves submerged in 2-chloroprocaine and the mixture of 2-chloroprocaine and bupivacaine was greater than that observed in nerves immersed in control solution, lidocaine, or bupivacaine. No difference between damage scores in any zone was found when lidocaine and bupivacaine were compared with control solution.

The impact of the presence of epinephrine on the
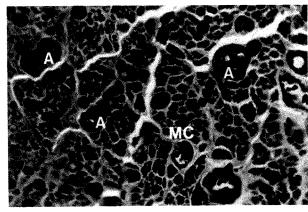
Fig 2. Micrographs of transverse sections from specimens of vagus nerve excised 12 days after exposure of carotid sheath to local anesthetic solution. (Epon sections stained with azure blue.) Solutions and numerical damage scores were as follows: top, lidocaine, 2 g/dl, and epinephrine, 5 μg/ml, showing normal epineurium (EP), questionable perineurial fibrosis (PF): score 1, and normal endoneurium (EN) and axons: score 0. Magnification 257×. Middle, 2-Chloroprocaine, 3 g/dl, and epinephrine, 5 μg/ml, showing cellular infiltration and fibrosis of epineurium (CI&F): score 3, perineurial fibrosis (PF): score 4, and abnormal axons (AX). Magnification 257×. Bottom, 2-Chloroprocaine, 3 g/dl, and epinephrine 5 μg/ml. Enlarged portion of same specimen as middle figure, showing macrophage transformation of Schwann cell (MC) and numerous degenerating axons (A). Magnification 411×.

FIG 4. Average damage scores in epineurial (A), perineurial (B), and axonal (C) zones of nerves specimens obtained 12 days after exposure to physiologic salt solution Medium 199 (control) and to 2-chloroprocaine, 3 g/dl (CLP). In all zones damage scores were greatest in nerves exposed to 2-chloroprocaine. Presence of epinephrine, 5 μg/ml, increased damage score.

damage scores is shown in Fig 4, and the probabilities resulting from two-way analysis of variance are presented in Table 3. 2-Chloroprocaine was associated with significantly greater damage in all zones than control solution. Epinephrine increased the damage in all zones, but an interaction effect (potentiation) was observed only in the outer, epineurial zone.

Discussion

The cervical part of the vagus nerve of rabbit was chosen for this study in vivo because it is readily amenable to standardized treatment and observation. The fiber composition of this nerve is similar to that of human vagus (15) and of cutaneous sensory nerves (16).

The results of this study show that application to the carotid sheath (containing the vagus nerve) of 3% 2-chloroprocaine and epinephrine, 5 μg/ml, or a mixture of 1.5% 2-chloroprocaine and 0.375% bupivacaine and epinephrine, 5 μg/L, frequently impaired C-fiber conduction and caused a high incidence of histologic abnormalities, including epineurial cellular infiltration and fibrosis, perineurial fibrosis, and axonal de-

FIG 3. Average damage scores in three zones of vagus nerve (mean ± SEM). Probability values are results from one-way analysis of variance using linear contrasts. LID = lidocaine, 2

g/dl; BUP = bupivacaine 0.75, g/dl; CLP = 2-chloroprocaine, 3 g/dl. Mixture = 2-chloroprocaine, 1.5 g/dl, and bupivacaine, 0.375 g/dl, CLP. All solutions contained epinephrine, 5 μg/ml.

TABLE 3

Probability Values Associated with Treatment Effects In Two-Way Analysis of Variance

	Chloropro-caine	Epinephrine	Interaction
Epineurial damage	<0.001	0.002	0.017
Perineurial damage	<0.001	0.010	0.053
Axonal damage	<0.001	0.010	0.068

generation. The adverse effect on nerve function and structure did not seem to be related to the acidity of the 2-chloroprocaine solution as neural damage was not diminished by neutralization. The acid pH of the 2-chloroprocaine solution (pH = 3.3) has been thought to cause the adverse neurologic reaction reported following the inadvertent subarachnoid injection of a large volume of 2-chloroprocaine (17). The present findings do not support this mechanism.

The rapid development of pinpoint hemorrhages in the tissues exposed to 2-chloroprocaine-containing solutions and their steady increase in size during the exposure suggest an adverse effect of 2-chloroprocaine on blood vessels or red cells. Harris et al (18) have reported increased incidence of venous thrombosis following intravenous regional anesthesia with 2-chloroprocaine and have suggested that the causal mechanism is vasculitis.

An older neuropathologic study of local anesthetics in the rat (12) found no abnormalities resulting from exposure to a variety of local anesthetic agents including 2-chloroprocaine. However, that study was restricted to 2-chloroprocaine 1% concentration without epinephrine, and a nerve conduction test was not performed.

The neurotoxic effect observed in this study could be due to the drug itself, or the antioxidant (sodium bisulfite) present in 2-chloroprocaine (Nesacaine-CE) or to both. The effect of sodium bisulfite alone was not evaluated in this study (but see Fig 1). The addition of epinephrine to 2-chloroprocaine solution increased the incidence of histologic abnormalities. It is known that the intraneural concentration of local anesthetic varies directly with the total amount of drug and the total volume of solution injected (19). It has also been shown that the presence of epinephrine in the anesthetic solution increases the intraneural concentration of lidocaine and amount retained in the nerve at the end of 2 hours following the injection (20), and increases the incidence of axonal degeneration (21). Moore (22) has advised caution in the use of high concentration of lidocaine and mepivacaine with epinephrine in peripheral nerve blocks. How-

ever, many other factors probably also affect the intraneural concentration and its change over time, including duration of exposure, nerve size, and regional blood flow.

The relation of neurotoxicity to neural concentration of local anesthetic is unclear. It is known that local anesthetic drugs inhibit oxidative metabolism (23). Ngai et al (24) suggested that the irreversible inhibition of the rapid axonal transport that results from interference with the energy requirement and the metabolic need of the nerve is an indicator of neurotoxicity. However, the critical degree of sensitivity of rapid axonal transport to local anesthetic is unsettled (24).

Peripheral nerve function seems to be dependent on a special perineurial and endoneurial milieu (25) and could be influenced by changes in the epineurium and the tissue surrounding the nerve. In the present study, an extraneural and epineurial tissue reaction occurred following exposure to 2-chloroprocaine and epinephrine solution that consisted of extensive cellular infiltration and thickening of the epineurium and marked perineurial fibrosis. Foster and Carlson (26) surveyed the myotoxicity to the rat tibialis muscle of seven commercial preparations of local anesthetics. Effects confined to muscle fibers were observed following the administration of lidocaine and bupivacaine, but an additional effect on vasculature, including the development of a prominent zone of ischemic necrosis, followed the administration of 2-chloroprocaine 2% and lidocaine 0.5% with epinephrine 1:200,000. Ravindran et al (27) recently reported that subpial necrosis developed in 13 or 15 dogs following subarachnoid administration of 2-chloroprocaine, but not following bupivacaine.

The tissue reaction in group 5 (2-chloroprocaine 1.5% and bupivacaine 0.375% and epinephrine, 5 μg/ml) was as significant statistically as in group 4A (2-chloroprocaine 3% and epinephrine, 5 μg/ml) (Fig 4). Although this might seem to suggest that even 1.5% 2-chloroprocaine may be neurotoxic, this suspicion should be suspended until the part played by each component in the mixture has been determined.

In the present study in a laboratory animal model, 2-chloroprocaine was found to be more neurotoxic than clinically equivalent solutions of lidocaine and bupivacaine. Further work is needed to clarify the clinical relevance of these observations.

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Age and Fentanyl Pharmacokinetics

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Fentanyl pharmacokinetics was compared in two groups of adult patients, one group (n = 5) aged <50 years, and one
group (n = 4) aged > 60 years. Despite equivalent doses of fentanyl (10 µg/kg IV), serum drug concentrations were
significantly higher in the older patient group. This was reflected by a prolonged terminal elimination half-life in the
elderly compared with the younger patients (945 versus 265 minutes, respectively, $p < 0.005$). Volumes of the central
compartment and volumes of drug distribution were similar in both patient groups. However, drug clearance was
markedly decreased in the elderly (265 versus 991 ml/min, $p < 0.005$). These data suggest that a given dose of
fentanyl will be clinically effective for a longer period in older patients than in younger patients.

PREVIOUS investigations indicate that changes in morphine and meperidine pharmacokinetics may occur with increasing age. Stanski et al (1) reported a terminal elimination half-life for morphine of 2.9 hours in young, healthy volunteers as contrasted to 4.5 hours in patients 61 years or older undergoing aortic aneurysm resection. Furthermore, Chan et al (2) reported that serum concentrations of meperidine were higher in patients older than 70 years of age compared with patients less than 30 years of age. With this background, we investigated fentanyl pharmacokinetics in adult patients less than age 50 years and elderly patients older than 60 years of age.

Methods

Nine consenting female patients ranging in age from 29 to 73 years were studied using a protocol approved by the Human Subjects Committee at the University of Arizona Health Sciences Center. All patients were scheduled for elective intra-abdominal surgery. Each patient was premedicated with 10 mg of oral diazapam and 0.2 mg of intramuscular glyco-

pyrrolate 1 to 1.5 hours before surgery. Anesthesia was induced with 200 to 400 mg of intravenous thiopental followed by 60 to 100 mg of succinylcholine to facilitate tracheal intubation. Following induction, 10 µg/kg of fentanyl was administered as an intravenous bolus. Arterial blood samples were then collected at 1, 2, 5, 10, 15, and 30 minutes and then at 30-minute intervals for 7 hours after initial drug administration. Serum fentanyl concentrations were subsequently determined by the method of Gillespie et al (3). The assay is sensitive to 0.1 µg/ml with coefficients of variation of 5.6% and 9.1% at fentanyl concentrations of 1.0 µg/ml and 0.25 µg/ml, respectively. Maintenance of anesthesia included 60% nitrous oxide in oxygen and incremental doses of thiopental (25 to 50 mg) as necessary to ensure amnesia. Pancuronium bromide was utilized for skeletal muscle relaxation and ventilation was mechanically controlled. Intraoperative and postoperative Pa_{CO_2} levels were not determined.

Serum fentanyl concentration versus time data were analyzed by computer using weighted $(1/y^2)$ nonlinear least-squares regression analyses (4). Initial estimates of pharmacokinetic equations were obtained by application of the method of residuals (5). Two- or three-compartment pharmacokinetic modeling was based on the F ratio testing criteria of Boxenbaum et al (6).

Student's *t*-test was used to compare group mean values, whereas linear correlation was used to analyze

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changes in pharmacokinetics parameters with age. Statistical significance was defined as $p < 0.05$.

Results

As can be seen in Table 1, weight, height, fentanyl dose, and anesthesia time (induction to recovery room arrival) were similar in both groups of patients. However, age differed between the two patient groups as a result of study design.

Each individual serum concentration time curve was best described by a triexponential equation corresponding to a three-compartment, open-mamillary model. Representative individual curves for both patient groups are shown in Fig 1. Secondary increases

TABLE 1
Group Characteristics*

	Adult	Elderly
No. of patients	5	4
Age (yr)	36 ± 4	67 ± 2†
Weight (kg)	64 ± 3	68 ± 7
Height (cm)	165 ± 3	165 ± 3
Fentanyl dose (μg)	642 ± 31	676 ± 66
Anesthesia time (min)	169 ± 29	150 ± 20

* Values are means ± SEM.

† Group mean values significantly different, $p < 0.001$.
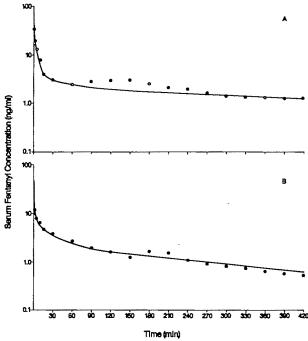
Fig 1. A, Serum fentanyl concentration plotted as function of time in a 65-year-old patient; B, same for younger patient, 33 years old. Secondary increases in serum concentrations can be seen in both patients. Terminal elimination half-lives in the older and younger patients are 720 and 266 minutes, respectively.

in serum fentanyl concentrations were seen in three elderly and four of the younger patients.

Despite equivalent fentanyl dosing (micrograms per kilogram of body weight), serum concentrations were higher in the older patients (Fig 2). This resulted from a prolonged terminal elimination half-life ($t_{1/2\beta}$) in the elderly compared with the younger patients (945 and 265 minutes, respectively, $p < 0.005$). In contrast, the drug distribution half-lives ($t_{1/2\pi}$ and $t_{1/2\alpha}$) were similar in the two patient groups (Table 2). In addition, the volume of the central compartment (Vc) was similar in the two groups of patients, although the mean absolute value tended to be lower in the elderly (Table 2). As a result, initial mean serum concentrations of fentanyl were higher in the elderly (Fig 2).

The volume of distribution (Vd) was the same in both patient groups, but drug clearance (Cl) was
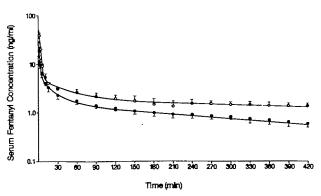
Fig 2. Mean ± SEM serum concentration time curve in four elderly (O) and five younger patients (●) given 10 μg/kg of intravenous fentanyl. Upper and lower curves can, respectively, be described by the triexponential equation $C_{S(t)} = 46e^{-0.474t} + 3.3e^{-0.0215t} + 1.80e^{-0.000749}$ and $C_{S(t)} = 30e^{-0.576t} + 3.6e^{-0.0413} + 1.52e^{-0.00244t}$. This represents fentanyl terminal elimination half-life of 925 minutes in elderly and 284 minutes in younger patients.

TABLE 2
Fentanyl Pharmacokinetics*

	Adults	Elderly
$t_{1/2\pi}$ (min)	1.36 ± 0.44	1.67 ± 0.38
$t_{1/2\alpha}$ (min)	28 ± 8	39 ± 8
$t_{1/2\beta}$ (min)	265 ± 22	945 ± 64†
Vc (L)	24 ± 7	17 ± 6
Vc (L/kg)	0.36 ± 0.09	0.23 ± 0.06
Vd (L)	381 ± 55	328 ± 27
Vd (L/kg)	5.9 ± 0.8	4.9 ± 0.5
Cl (ml/min)	991 ± 111	275 ± 57†
Cl (ml/min/kg)	15.4 ± 1.6	4.0 ± 0.6†

* Values are means ± SEM. Abbreviations used are: $t_{1/2\pi}$, drug distribution half-life; $t_{1/2\alpha}$, drug distribution half-life; $t_{1/2\beta}$, elimination half-life; Vc, central compartment volume; Vd, volume of distribution, Cl, clearance.

† Group mean values significantly different, $p < 0.005$.

decreased in the elderly (Table 2). Significant correlations were found between age and both $t_{1/2\beta}$ and clearance ($r = 0.82$, $p < 0.01$ and $r = -0.80$, $p < 0.05$, respectively), but not between age and Vd.

Discussion

This study demonstrates that fentanyl pharmacokinetics changes with age. After comparable doses of fentanyl (micrograms per kilogram of body weight), serum drug concentrations were higher in elderly than in younger patients. This is a result of a prolonged terminal elimination half-life ($t_{1/2\beta}$) in the elderly, not changes in fentanyl distribution (Vc, $t_{1/2\pi}$, $t_{1/2\alpha}$). Alterations in $t_{1/2\beta}$ can result from changes in Vd or clearance as $t_{1/2\beta} = 0.693$ Vd/Cl (5). In this study, Vd did not change with age, but clearance did. Thus, the prolonged $t_{1/2\beta}$ in the elderly was due to decreased drug clearance.

Decreased fentanyl clearance in the elderly might be a result of several factors, including decreases in hepatic blood flow or hepatic microsomal enzyme activity or increases in drug protein binding (7). Although none of these variables was measured in this study, alterations in each have been documented with aging. For example, hepatic blood flow decreases with aging (8). Furthermore, the metabolic clearance of antipyrine, an index of microsomal enzyme activity, has consistently been shown to be decreased in the elderly (9, 10). Lastly, there is also a linear decrease in serum albumin levels with age (11). Fentanyl pharmacokinetics could be altered as a result since fentanyl is extensively bound to albumin (12). However, altered protein binding alone should have little or no effect on fentanyl clearance as the drug has such a high hepatic clearance (13). More likely, decreases in protein binding would be manifest by an increase in Vd and potentially $t_{1/2\beta}$ as $t_{1/2\beta} = 0.693$ Vd/Cl (14). As the Vd of fentanyl was similar in the older and younger patients in our study, probably fentanyl protein binding was also similar in the two groups of patients.

Previous investigations also indicate that pharmacokinetics of other narcotics is altered in the elderly. Chan et al (2) reported serum concentrations of meperidine that were higher in elderly patients than in patients less than age 30 years. Mather et al (15) also reported positive correlation of the free fraction of meperidine in plasma as a function of age. This would result in even higher free meperidine concentrations in the elderly patients than those reported by Chan et al (2).

Morphine disposition also may be altered with

aging. Stanski et al (1) reported a prolonged $t_{1/2\beta}$ in four elderly patients undergoing aortic aneurysm resection compared with healthy volunteers (mean age 28 years). In contrast, Berkowitz et al (16) found initial serum morphine concentrations were higher in patients older than 50 than in patients younger than 50 years of age. However, $t_{1/2\beta}$ was similar in the two patient groups. Thus, the effect of age, if any, on morphine pharmacokinetics is unclear.

The secondary peaks in serum fentanyl concentration seen in four of our younger patients and three of our older patients have been described previously by others. Stoeckel et al (17) have shown that fentanyl is sequestered in the gastric juice, presumably because of ion trapping. They postulated that the sequestered fentanyl is subsequently absorbed from the small intestine to cause secondary peaks in the serum concentration-time curve. We feel that this is unlikely, as we have previously noted secondary fentanyl peaks in morbidly obese patients despite continuous nasogastric suctioning (18). In addition, the high systemic clearance of fentanyl suggests that drug absorbed from the gastrointestinal tract would be subject to extensive first-pass metabolism. Another mechanism that could explain these peaks may be sequestration in muscle with subsequent release on resumption of activity. Yet, secondary peaks were seen in some of our patients before the termination of surgery and thus this mechanism also is not tenable. A more likely explanation is that fentanyl trapping occurs in the lung because of altered ventilation-perfusion relationships during surgery and anesthesia. As these relationships return toward normal, fentanyl is washed out of the lung resulting in secondary fentanyl peaks. This speculation is plausible as fentanyl lung storage is large (19) and lung ventilation and perfusion relationships change during surgery and anesthesia (20).

In summary, this study demonstrated higher serum concentrations of fentanyl in elderly patients than in younger patients despite equivalent (micrograms per kilogram of body weight). The prolonged fentanyl elimination in the older patients results primarily from decreased drug clearance. The findings in this study suggest that a given dose of fentanyl will last longer in older patients than in younger patients.

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Fentanyl Infusion Anesthesia for Aortocoronary Bypass Surgery: Plasma Levels and Hemodynamic Response

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Plasma fentanyl concentrations were measured by radioimmunoassay in patients during aortocoronary bypass surgery and correlated with hemodynamic responses to surgical stimulation. Thirty patients scheduled for aortocoronary bypass surgery were divided into three groups of 10. Patients in group 1 received fentanyl, 30 μg/kg, as a loading dose followed by an infusion of 0.3 μg/kg/min; those in group 2 received 40 μg/kg as a loading dose followed by an infusion of 0.4 μg/kg/min; and those in group 3 received 50 μg/kg as the loading dose followed by an infusion of 0.5 μg/kg/min. The total dose of fentanyl administered to each group up to the time of rewarming on cardiopulmonary bypass was 60 μg/kg, 90 μg/kg, and 100 μg/kg, respectively. Each of the dose regimens produced stable plasma concentrations starting approximately 20 minutes after induction and continuing until the infusion was discontinued. Patients in group 1 had a mean plasma concentration of 10 to 12 ng/ml in the stable period compared with 12 to 14 ng/ml in group 2 and 15 to 18 ng/ml in group 3. Fewer patients in group 3 responded to intubation and surgical stimulation than in the other groups, although the differences between groups were not statistically significant. Response to stimulation was treated by the administration of droperidol or volatile anesthetic agents. At a plasma concentration of 15 ng/ml, 50% of patients had an increase in systolic blood pressure which required treatment. This minimal intra-arterial concentration, analogous to MAC, can be achieved by the administration of fentanyl as a loading dose of 50 μg/kg followed by an infusion of 0.5 μg/kg/min.

Key Words: ANESTHETICS, Intravenous: fentanyl; ANESTHESIA: cardiovascular; PHARMACOKINETICS: fentanyl.

FENTANYL-OXYGEN anesthesia is an established anesthetic technique for patients undergoing cardiac surgery. Advantages include ease of administration, satisfactory anesthesia, cardiovascular stability,

and modification of the stress response to surgery (1–6). Disadvantages include truncal rigidity (3), prolonged respiratory depression (7), postoperative awareness (4, 8), and in some instances, hemodynamic instability (3, 4).

In previous studies (1–5) of fentanyl-oxygen anesthesia for cardiac surgery, fentanyl was administered as a bolus or as a short infusion to a dose of 50 to 100 μg/kg. Plasma fentanyl concentrations between 25 and 48 ng/ml achieved with 75 μg/kg as a short infusion have produced stability of hemodynamic function before institution of cardiopulmonary bypass (1). However, hypertension and tachycardia in response to noxious stimuli during aortocoronary bypass surgery have been reported after doses of 60 μg/kg of fentanyl (3) and even after fentanyl, 100 μg/kg, administered as a bolus, particularly at the time of aortic root dissection (4). This suggests that a bolus or short infusion of fentanyl in doses up to 100 μg/kg,

although initially producing brain concentrations sufficient to prevent adverse hemodynamic responses to early surgical stimulation, does not produce plasma and brain concentrations of fentanyl adequate to produce complete anesthesia up to the time of cardiopulmonary bypass. Hug and Murphy (9) have shown in rats that brain concentrations of fentanyl are 2 to 4 times higher than plasma concentrations and their decline parallels the decrease in plasma concentrations. This decline could account for apparent inadequate anesthesia observed in some patients at the time of aortic root dissection. We wished to determine whether up to 100 μg/kg of fentanyl administered by various loading doses and infusion rates would produce stable plasma fentanyl concentrations above which hemodynamic responses to surgery were obtunded.

Methods

The study was approved by the Ethics Committee of the Royal Victoria Hospital. Thirty patients scheduled for aortocoronary bypass surgery were divided into three groups of 10, each with comparable demographic data (Table 1). All patients were maintained on their medications until the night before surgery with the exception of beta-adrenergic inhibi-

TABLE 1

Demographic Data of Fentanyl Infusion Groups

	Group 1 bolus, 30-μg/ kg; infusion, 0.3 μg/kg/min	Group 2 bolus, 40 μg/kg; infusion, 0.4 μg/kg/min	Group 3 bolus, 50 μg/ kg; infusion, 0.5 μg/kg/min
Age (mean yr ± SEM)	57.1 ± 4.8	55 ± 7	59.2 ± 7.9
Sex (male/female)	9/1	8/2	10/0
Preoperative medications			
Digoxin	3	1	1
Propranolol	10	8	8
NTG	7	5	5
Diuretic	3	4	3
Antihypertensive	0	0	2
Preoperative cardiac catheterization			
Diseased vessels			
1	0	0	1
2	1	2	1
3	9	8	8
Ventricular function			
Normal	6	8	8
Mild-moderate dysfunction	4	2	2

tors and nitrate preparations which were continued to the time of operation. Patients were premedicated with diazepam, 0.15 mg/kg, orally and morphine, 0.15 mg/kg, and scopolamine, 0.4 mg, intramuscularly 1 hour before induction of anesthesia. Patients in group 1 received 30 μg/kg of fentanyl intravenously as a loading dose followed by an infusion of 0.3 μg/kg/min; those in group 2 received 40 μg/kg as a loading dose and an infusion of 0.4 μg/kg/min; and those in group 3 received 50 μg/kg as a loading dose followed by an infusion of 0.5 μg/kg/min. We studied patients in group 2 first, followed by group 3 and group 1. Investigator bias was minimized by studying consecutive patients with good ventricular function and completing each group before starting the next. All patients breathed oxygen administered by nasal prongs while intravenous, intra-arterial, and thermodilution pulmonary arterial catheters were inserted under local anesthesia. A modified V_5 electrocardiogram was monitored throughout surgery. A control hemodynamic profile was determined before induction of anesthesia using a Texas Instrument TI 59 programmable calculator with standard formulas and was repeated following the loading dose of fentanyl given at the rate of 1 mg/min. Further hemodynamic profiles were obtained after intubation, skin incision, sternotomy, and, when possible, aortic root dissection. Monitoring equipment consisted of Bentley Trantec Transducers, a General Electric Four Traces monitor, and an Edwards Laboratory cardiac output monitor (model 9520A).

The fentanyl infusion was given by a previously calibrated Harvard infusion pump. The infusion was started as soon as the loading dose had been given and was continued until rewarming had commenced on cardiopulmonary bypass or until the patient had received a total of 100 μg/kg. Fentanyl induction was preceded by 1 to 2 mg of pancuronium to prevent chest wall rigidity (4). Upon loss of consciousness, muscle paralysis was secured with additional pancuronium to a total dose of 0.15 mg/kg. Patients were then intubated and ventilated with 100% oxygen using a modified T-piece to maintain normocarbia.

Blood samples for fentanyl measurements were taken in polypropylene tubes at 5, 10, 20, and 30 minutes and then every half hour from the beginning of the induction of anesthesia. All samples from a single infusion study were assayed in the same run. Plasma fentanyl concentrations were measured by a sensitive radioimmunoassay (RIA) using the fentanyl RIA kit (10). Duplicate tubes containing 2- to 20-μl plasma samples or standard solutions of fentanyl

(0.005 to 2 assay tube) were incubated with antibody and ^{3}H fentanyl for 2 hours at 22°C (total incubation volume 0.7 ml). ^{3}H fentanyl was separated from antibody-bound ^{3}H fentanyl using 2% dextran-coated charcoal. The supernatant radioactivity representing antibody-bound ^{3}H fentanyl was quantitated using a Packard beta spectrophotometer. Under these conditions 35% to 40% of total counts added were bound to the antiserum. Nonspecifically bound radioactivity was monitored in non-antibody-containing control tubes and was less than 2% of counts added both in the presence or absence of serum. Results of assays including assay sensitivity and precision were calculated using the computer program of Faden and Rodbard (11). Mean assay sensitivity for 22 consecutive assays was 5.8 ± 0.3 pg (range 3.9 to 8.9 pg). Within assay precision, expressed as a coefficient of variation, was ±3%. Between assay precision was ±10%. Hemolyzed samples were found to interfere in the RIA giving spuriously high values. This effect was minimized by dilution of samples before assay so that the volume included in the RIA was no greater than 5 μl of the original sample.

An increase in heart rate or blood pressure of 20% or more over the previous recording was termed a "response." When a response occurred, it was treated either with various supplemental anesthetic agents including N_2O, droperidol, and enflurane, or, at times, in combination with intravenous nitroglycerin. The time at which a response occurred was recorded and related to the plasma fentanyl concentration.

Data were analyzed for statistical significance using Student's t-test and the exact probability test of Fisher, Irwin, and Yeats.

Results

The mean plasma fentanyl concentrations in patients in groups 1, 2, and 3 in the 20- to 180-minute period were 10 to 12 ng/ml, 11 to 14 ng/ml, and 15 to 18 ng/ml, respectively. These concentrations were significantly different between groups 1 and 3 in the 5- to 30-minute time intervals. Thereafter there were no statistically significant differences in the mean plasma concentrations of fentanyl between the groups. However, from Fig 1 it can be seen that for the first 90 minutes there appears to be a trend for the patients who received the highest infusion rate to have the highest plasma levels. Subsequently, plasma fentanyl concentrations in patients in group 3 approached those observed in patients in group 2, and by 180 minutes patients in group 1 had the highest
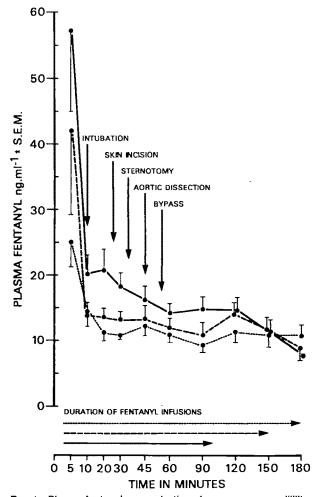
Fig 1. Plasma fentanyl concentrations (nanograms per milliliter ± SEM) and duration of fentanyl infusions in each group: group 1; . . . ., group 2, - - -, group 3, ——.

concentrations. Because the total dose of fentanyl was limited to 100 μg/kg, patients in group 1 received the infusion for approximately 230 minutes, those in group 2 for approximately 150 minutes, and those in group 3 for approximately 100 minutes. For all patients in group 1 and for the majority of patients in group 2 the infusion was stopped when rewarming was begun on bypass and before they had received a total of 100 μg/kg. Plasma fentanyl concentrations decreased an average of 30% when cardiopulmonary bypass was instituted but returned to their approximate pre-bypass values within 30 minutes. The mean time at which cardiopulmonary bypass was begun was 55 minutes following induction of anesthesia so that all patients were still receiving a fentanyl infusion 30 minutes after the beginning of bypass.

The cumulative number of patients and the points at which they responded are shown in Fig 2. Of the
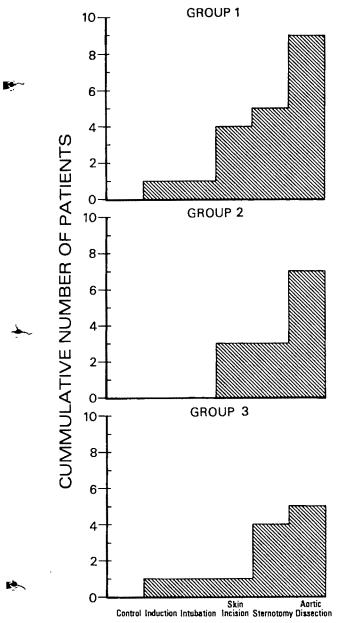
Fig 2. Cumulative number of patients responding to induction of anesthesia and surgical stimulation before cardiopulmonary bypass.

patients in group 1, one received supplemental droperidol to induce unconsciousness, three responded to skin incision, one at sternotomy, and four at aortic root dissection. Of the 10 patients in group 2, three responded to skin incision and four to aortic root dissection. In group 3, one patient had more than a 20% increase in heart rate at the time of induction, whereas three patients responded to sternotomy and one to aortic root dissection. These results suggest

that patients receiving the higher dose respond less frequently and later than those receiving the lower dose, although there is no statistically significant difference between the 9, 7, and 5 responses in each group.

Hemodynamic measurements and derived indices in the three groups are shown in Table 2. No significant differences between the groups were demonstrated. In addition, each event was compared to its control and to the previous event within each group regardless of whether supplemental anesthesia was administered or not. No changes from control values were noted in central venous pressure, pulmonary capillary wedge pressure, or left ventricular stroke work index within any group. Significant changes in heart rate, cardiac index, and systemic vascular resistance occurred in group 1. In group 2, significant changes were seen in heart rate, systolic blood pressure, and systemic vascular resistance, whereas in group 3 such changes were only seen in heart rate. Thus, patients who received the highest dose of fentanyl had fewer significant hemodynamic changes.

One patient in group 1 could remember his leg being incised for the donor vein but denied discomfort. His systolic blood pressure increased by more than 20% and additional anesthesia was given for the remainder of the surgical procedure.

At the time of this study, it was our policy to ventilate patients overnight after surgery and no patient required mechanical respiratory support beyond this time.

Discussion

Previous reports have suggested that the incidence of hemodynamic disturbances during aortocoronary bypass surgery using fentanyl-oxygen anesthesia decreases when the dose of fentanyl is increased (4). In doses of 50 μg/kg, significant increases in systolic blood pressure and systemic vascular resistance were observed at the time of tracheal intubation, skin incision, and sternotomy (3). When the dose was increased to 100 μg/kg, hemodynamic changes were less frequent and additional anesthesia was usually only necessary at the time of aortic root dissection (4). This suggests that the higher dosage produced brain concentrations of narcotic sufficient to effect anesthesia for a longer time but still insufficient to inhibit cardiovascular responses up to the time of cardiopulmonary bypass.

In the present study, total doses of fentanyl varied between 50 and 100 μg/kg because the infusion was

TABLE 2

Hemodynamic Data during Fentanyl-Oxygen Anesthesia in Three Groups of Patients Undergoing Aortocoronary Bypass Surgery*

	HR	SBP	CVP	PCWP	CI	LVSWI	SVR
	beats/min		torr		$L/min/m^2$	$q \cdot m/m^2$	units
Control							
1	62 ± 3	115 ± 4	6 ± 1	11 ± 1	2.8 ± 0.2	47 ± 3	128 ± 7
2	66 ± 3	123 ± 3	8 ± 1	12 ± 1	3.3 ± 0.2	57 ± 6	116 ± 7
3	62 ± 2	126 ± 7	6 ± 2	8 ± 2	3.0 ± 0.2	53 ± 6	113 ± 10
Induction							
1	77 ± 3†‡	116 ± 3	8 ± 1	13 ± 2	3.5 ± 0.2†‡	48 ± 3	104 ± 5†‡
2	74 ± 3	108 ± 6†‡	8 ± 1	12 ± 1	3.6 ± 0.2	48 ± 6	94 ± 4†‡
3	72 ± 4†‡	117 ± 8	8 ± 2	10 ± 2	3.6 ± 0.5	53 ± 5	109 ± 15
Intubation							
1	79 ± 3†	122 ± 4	7 ± 1	11 ± 1	3.6 ± 0.2†	52 ± 3	107 ± 7†
2	77 ± 3†	114 ± 5	7 ± 1	10 ± 1	3.6 ± 0.3	50 ± 6	103 ± 7
3	77 ± 5†	115 ± 6	6 ± 1	8 ± 1	3.5 ± 0.3	46 ± 3	110 ± 15
Skin incision							
1	69 ± 2‡	127 ± 6	6 ± 1	10 ± 2	3.2 ± 0.2	55 ± 4	130 ± 9
2	67 ± 4	117 ± 6	8 ± 2	11 ± 2	3.1 ± 0.3	50 ± 8	125 ± 16
3	71 ± 4	116 ± 6	7 ± 2	9 ± 1	3.2 ± 0.3	49 ± 5	109 ± 12
Sternotomy							
1	72 ± 3†	125 ± 5	6 ± 1	9 ± 2	3.0 ± 0.3	48 ± 4	138 ± 11
2	73 ± 3	124 ± 6	8 ± 2	9 ± 1	2.7 ± 0.2	43 ± 4	140 ± 12
3	70 ± 4	128 ± 5	6 ± 1	9 ± 1	3.4 ± 0.4	55 ± 6	112 ± 11
Aortic root dissection							
1	77 ± 5†	129 ± 11	6 ± 2	8 ± 2	3.4 ± 0.5	46 ± 3	127 ± 22
2	75 ± 4	135 ± 8					
3	71 ± 4	131 ± 7					

* Values are means ± SEM. Abbreviations used are: HR, heart rate; SBP, systolic blood pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; LVSWI, left ventricular stroke work index; and SVR, systemic vascular resistance.

† $p < 0.05$ compared with control values.

‡ $p < 0.05$ compared with previous study period.

stopped either at the start of rewarming before discontinuation of cardiopulmonary bypass or when a total of 100 μg/kg had been given. The administration of fentanyl by infusion allowed its continuous administration during cardiopulmonary bypass and was only stopped in group 1 (total dose 60 μg/kg) and group 2 (total 90 μg/kg) at rewarming, approximately 2 hours after induction of anesthesia.

We used the pharmacokinetic model of McClain and Hug (12) to predict plasma fentanyl concentrations following the combination of intravenous bolus and infusion and we assumed that the pharmacokinetic parameters were independent of dose. Steady-state plasma concentrations during an infusion, when the concentrations of drug in blood and at its site of action are in equilibrium, are achieved only after four to five elimination half times, i.e., 15 to 18 hours for fentanyl. Our combined techniques maintains stable plasma concentrations after only 20 to 30 minutes. Initially, the contribution of the infusion to the plasma

concentration is small, only 6% of the eventual steady-state concentration at 20 minutes, but the contribution increases with time, e.g., 16% at 60 minutes. The plasma fentanyl concentrations obtained in this study were 1½ to 2 times higher than predicted (12), but were comparable to those obtained by Bovill and Sebel (13) and Schleimer et al (14). We believe that our values for fentanyl are more accurate than those reported by others for two reasons. First, the recommended volume of plasma sample in the RIA kit is 50 μl. This amount is generally too much and results in fentanyl values that must be read from the lower end of the standard curve. Values calculated from this region of the standard curve tend to be imprecise and result in spuriously elevated concentrations. We have an exquisitely sensitive assay in which sample volumes as small as 2 to 20 μl are required for values to fall in the linear and more accurate part of the standard curve. Second, we have significantly reduced the effect of hemolysis by dilution of samples. Hemolyzed

samples caused nonspecific inhibition of tracer binding to antibody in the RIA giving rise to falsely high values. For example, plasma from a hemolyzed sample of blood containing no fentanyl gave a spurious reading of 48 ng/ml of fentanyl when assayed by RIA at a volume of 50 μl, whereas 2.5 μl of the same sample gave a value of 1 ng/ml. Other reasons for the differences in reported plasma fentanyl concentrations may be explained by different administration regimens or by altered pharmacokinetic behavior in this group of elderly patients with cardiac disease (15, 16). The discrepancy between actual and predicted plasma concentrations was not unexpected, but the simple formula used in the study did produce stable concentrations in individual patients.

Lunn et al (1), using an infusion of fentanyl at 300 μg/min to a total of 75 μg/kg, reported plasma concentrations greater than 25 ng/ml 105 minutes after the start of the infusion; these concentrations were associated with hemodynamic stability up to the time of cardiopulmonary bypass. Thus, a plasma concentration of 25 ng/ml produced brain concentrations sufficient to inhibit adverse hemodynamic responses to surgical stimuli before cardiopulmonary bypass. In our study the number of patients who responded to stimulation decreased as the loading dose and infusion rate of fentanyl increased. There were greater variations within groups 1 and 2 in heart rate, systemic vascular resistance, systolic blood pressure, and cardiac index compared with group 3, although the absolute numbers of patients responding to stimulation were not significantly different between the three groups. We were unable to establish a relationship between plasma concentrations of fentanyl and patient response to the stimulation of skin incision, sternotomy, and aortic root dissection. However, at a plasma concentration of 15 ng/ml or less, 50% of patients had an increase in systolic blood pressure which required treatment. Therefore a minimal intra-arterial concentration of fentanyl, analogous to MAC (17), could not be identified clearly, but it supports a level of approximately 15 ng/ml. However, care must be taken in correlating hemodynamic responses with plasma concentrations in non-steady-state conditions because the concentrations at the active site, the brain, may differ from that in blood (9) and, furthermore, the relationship changes depending on the mode of administration of fentanyl. None of our patients responded during intubation, 10 minutes after induction of anesthesia, although the plasma concentration was decreasing at this time. However, it has been demonstrated in rats that although the decline in brain

concentration parallels the decrease in plasma concentration, the brain level remains considerably higher than that in blood (9).

In 19 of the 21 "responders" to stimulation, the response was diagnosed on the basis of a change in systolic blood pressure which was controlled either by the addition of nitrous oxide, nitroglycerin, droperidol (18), or volatile anesthetics (19). The presence of background fentanyl anesthesia greatly facilitated the control of systolic blood pressure by additional anesthetics when indicated and no patient in this series demonstrated deterioration of myocardial ischemia before initiation of cardiopulmonary bypass.

We conclude that hemodynamic stability is improved during fentanyl-oxygen anesthesia for aortocoronary bypass surgery by administration of fentanyl as a bolus followed by a continuous infusion. If the plasma fentanyl concentration is maintained at greater than 15 ng/ml, hypertension and tachycardia occur in less than 50% of patients and can be easily treated. These conditions can be achieved by administering fentanyl as a bolus of 50 μg/kg followed by an infusion of 0.5 μg/kg/min.

ACKNOWLEDGMENTS

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Myocardial Metabolism and Hemodynamic Responses to Halothane or Morphine Anesthesia for Coronary Artery Surgery

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MOFFITT, E. A., SETHNA, D. H., BUSSELL, J. A., RAYMOND, M., MATLOFF, J. M., AND GRAY, R. J.: Myocardial metabolism and hemodynamic responses to halothane or morphine anesthesia for coronary artery surgery. Anesth Analg 1982;61:979-85.

Eighteen patients having coronary artery bypass grafts were randomly anesthetized with morphine (1 mg/kg) or halothane and oxygen. Central and peripheral pressures were measured serially, plus cardiac output and total coronary sinus blood flow, both by thermodilution catheters, starting before induction of anesthesia and continuing until completion of sternotomy. No significant differences in hemodynamic responses were seen between the two anesthetic techniques during induction: blood pressure and peripheral vascular resistance decreased significantly, but not cardiac output or coronary flow. Myocardial oxygen consumption decreased significantly with induction as oxygen content of coronary sinus blood increased, indicating preservation of oxygen balance. Heart rate and blood pressure increased after sternotomy in the patients given morphine, with the myocardium producing lactate in two of six patients and with nitroprusside being required in four patients to decrease arterial pressure. Halothane-oxygen anesthesia effectively controlled autonomic responses to sternotomy, although one of 12 patients had myocardial lactate production at that time. Neither rate-pressure product or ST segment changes were useful predictors of the ratio between myocardial oxygen consumption and supply. Myocardial oxygen balance can be maintained in coronary patients before cardiopulmonary bypass if pulse rate and blood pressure are kept at less than awake levels.

Key Words: HEART: oxygen consumption; ANESTHESIA, cardiovascular; ANESTHETICS, Volatile: halothane; ANALGESICS: morphine.

H ALOTHANE and morphine have been widely used as the major anesthetic agents for coronary artery bypass grafting. Severe imbalances in myocardial oxygen supply and demand can, however, occur in such patients during anesthesia. Potent anesthetics may depress myocardial function and the circulation enough to reduce coronary blood flow and myocardial oxygen supply in patients with coronary

disease. Conversely, active sympathetic responses to surgical stimulation may cause myocardial oxygen needs to exceed supply in these patients. Knowledge is needed of the most rational and effective means for controlling sympathetic activity. In addition, it is important to know when oxygen supply is exceeded, i.e., when ischemia is present.

Although the systemic hemodynamic effects of halothane and morphine anesthesia have been described (1), the effects of these drugs on coronary hemodynamics and myocardial metabolism are not known in patients with obstructive coronary arterial disease. The goal of this study was to examine directly the effects of morphine or halothane anesthesia on the coronary circulation and myocardial energy metabolism in patients undergoing coronary artery bypass grafting (CABG), and to correlate these effects with systemic hemodynamic responses. This report covers the period from before anesthesia to initiation of cardiopulmonary bypass.

Methods and Materials

After informed consent was obtained, 18 patients in three groups of six, were studied with a protocol approved by our Human Subjects Committee. All patients had significant coronary arterial disease and were having CABG within 4 weeks of cardiac catheterization. Left ventricular ejection fraction was greater than 50% (mean 68%) in each patient, indicating normal left ventricular function. Left ventricular end-diastolic pressure (LVEDP) averaged 14 mm Hg (>20 mm Hg in four patients). Excluded from the study were patients with diabetes mellitus, valvular heart disease, arterial hypertension (diastolic > 105 mm Hg), significant pulmonary disease, and patients within 2 weeks after myocardial infarction. Patients with minimal mitral regurgitation were included. All patients had regular sinus rhythms.

The patients' average age was 58.8 years (range 41 to 73 years) and weight 76.8 kg (range 57 to 111 kg); 13 were men. Their New York Heart Classes (II, seven; III, eight; and IV, three) were evenly distributed in the groups. Thirteen patients had previous myocardial infarctions and 15 were taking propranolol. An average of 3.7 vein grafts were placed. There were no significant differences between the groups in terms of age, ejection fraction, LVEDP, or number of grafts.

The study was done in the operating room following instrumentation to be described. Measurements were made (a) before induction of anesthesia, (b) after induction, (c) after intubation, (d) before sternotomy, and (e) after sternotomy.

There were no modifications of preoperative medical regimen for the purpose of the study. In the operating room, using sedation and local anesthesia, we introduced: (a) a radial arterial cannula; (b) a thermodilution triple-lumen catheter (2) (Edwards, Santa Ana, CA) by the Seldinger technique through the right internal jugular vein into the pulmonary artery; and (c) a thermodilution catheter (Webster, Altadena, CA) by the same route and technique into the coronary sinus, aided by fluoroscopy (3).

All patients were premedicated with oral secobarbital (100 mg) the night before and 2 hours before surgery (3 mg/kg) to decrease anxiety.

All anesthetics were given by one of us (J.B.) and the 18 patients were randomly assigned to one of three protocols.

In six patients, anesthesia was induced with morphine sulfate, 1 mg/kg, 5 mg/min, followed by tracheal intubation after diazepam (mean 15.7 mg) to assure amnesia. The mean dose of morphine was 76.2

mg. Ventilation was assisted and later controlled to maintain Pa_{CO_2} at normal levels. The mean time from induction to intubation was 17 minutes.

In six patients (halothane group I) anesthesia was induced with halothane (up to 3%) in oxygen after an initial dose of thiopental (mean 135 mg). Blood pressure was reduced to 75% of awake value and maintained there for a mean time of 11 minutes before intubation. Respiration was assisted and controlled to keep Pa_{CO_2} normal. Intravenous morphine (0.25 mg/kg) had been given 45 minutes before induction.

In another six patients (halothane group II) halothane was used for induction as in group I, with inspired concentrations up to 3% for a mean time of 11 minutes before intubation. Patients in group II differed from those in group I in having morphine premedication intramuscularly (0.25 mg/kg) 1 hour before entering the operating room.

Pancuronium, 0.1 mg/kg, was used in all patients to facilitate tracheal intubation. After intubation, patients given morphine were ventilated with oxygen, whereas patients in the other two groups had halothane continued as needed to keep arterial pressure close to the awake value.

Total coronary sinus blood flow (CBF) was measured by thermodilution as described by Ganz et al. (3). Arterial and coronary sinus blood samples were obtained simultaneously for measurement of oxygen and lactate concentrations. Lactate was measured in duplicate by a modification of the Marbach method (4). Hemoglobin and its oxygen saturation were measured by co-oximetry (Instrumentation Laboratories, model 282). Systemic, pulmonary arterial, pulmonary capillary wedge (PCW), and right atrial pressures were recorded, along with the electrocardiogram, lead V_5 (Electronics for Medicine). Thermodilution cardiac outputs were measured in duplicate (Edwards). Hemodynamic indices were calculated from measured variables according to standard formulas.

Metabolic indices were calculated as follows: myocardial oxygen consumption (MV_{O_2}) in milliliters per minute = CBF × Art − CS difference of O_2 content with MV_{O_2} representing oxygen consumption of that portion of myocardium drained by the coronary sinus (CS, i.e., essentially the left ventricle).

Myocardial lactate extraction (MLE) in percent (Art − CS)/Art with Art and CS, the arterial and coronary sinus concentrations of lactate in milliequivalents per liter.

Statistical analysis was by analysis of variance, using the Newman-Keuls test, with $p < 0.05$ considered to be statistically significant. This test compares

the findings at each study time with those from all other series.

Results

There were no significant differences between the three groups in any measured or calculated variable at the same study time.

Hemodynamic and myocardial metabolic responses during morphine-oxygen anesthesia are summarized in Table 1. On induction, morphine caused a 22% reduction in systemic vascular resistance with a 27% decrease in mean arterial pressure ($p < 0.05$). This decrease in afterload was accompanied by only a small increase in heart rate and no significant change in cardiac index. The reduction in coronary perfusing pressure was accompanied by an 18% decrease in CBF ($p = $ NS). With a decrease in mean rate-pressure product from 7939 ± 844 to 6146 ± 300, there was a significant decrease in myocardial energy metabolism. The oxygen content of CS blood increased 25% ($p < 0.05$), which, with the modest decrease in CBF, resulted in a significant 40% decrease in MV_{O_2}. Myocardial lactate extraction remained normal during induction. Sympathetic responses accompanying laryngoscopy and intubation significantly increased mean arterial pressure (MAP) and heart rate, with

MV_{O_2} increasing as CS oxygen content decreased. The stress of sternotomy was less well tolerated hemodynamically and metabolically. Four patients required a nitroprusside infusion soon after the sternotomy to control the elevated blood pressure (after measurements called for in our protocol were obtained). Also, two patients showed myocardial lactate production after sternotomy, resulting in reduction in MLE for the group as a whole to essentially zero extraction.

Results in halothane group I are shown in Table 2. On induction, a 16% reduction in MAP and a 14% decrease in cardiac index was accompanied by a 34% decrease in MV_{O_2} ($p < 0.05$). The decrease in MV_{O_2} was reflected by an increase in CS oxygen content in the absence of changes in arterial oxygen content and CBF. Both pulse rate and blood pressure increased significantly on intubation, with an increase also in MV_{O_2}.

MLE did not change at any time. With halothane in oxygen given after intubation in concentrations necessary to keep the blood pressure at awake levels, other circulatory variables remained stable throughout. Likewise CBF, MV_{O_2} and MLE remained unchanged through the remainder of the period before initiation of cardiopulmonary bypass, including during sternotomy. As the chest was opened, there was a significant increase in mean PCW pressure.

TABLE 1

Hemodynamic and Myocardial Energy Metabolic Responses to Morphine*

	HR	MAP	SVR	PCW	CI	CBF	CS-O_2 content	MV_{O_2}	MLE
	beats/min	mm Hg	dynes·sec·cm^{-5}	mm Hg	L/min/m^2	ml/min	ml/dl	ml/min	%
Before induction	64 ± 5	85 ± 6	1386 ± 226	10 ± 1	2.6 ± 0.2	108 ± 8	7.4 ± 0.7	9.8 ± 0.3	35 ± 3
After induction	70 ± 3	62 ± 3†	1083 ± 132	10 ± 1	2.3 ± 0.2	89 ± 12	9.2 ± 0.7†	5.8 ± 0.7†	40 ± 9
After intubation	88 ± 5‡	84 ± 6‡	1239 ± 198	9 ± 1	3.0 ± 0.5	112 ± 26	7.9 ± 0.6‡	8.5 ± 1.7	42 ± 2
Before sternotomy	75 ± 3	95 ± 5	1389 ± 224	11 ± 1	3.0 ± 0.4	103 ± 8	6.8 ± 0.8	9.2 ± 0.9	20 ± 9
After sternotomy	81 ± 4	96 ± 7	1390 ± 151	14 ± 2	3.0 ± 0.4	103 ± 10	6.6 ± 0.6	8.9 ± 1.3	2 ± 21

* Values are means ± SEM; n = 6. Abbreviations used are: HR, heart rate; MAP, mean arterial pressure; SVR, systemic vascular resistance; PCW, pulmonary capillary wedge pressure; CI, cardiac index; CBF, coronary sinus blood flow; CS-O_2, coronary sinus oxygen; MV_{O_2} myocardial oxygen consumption; MLE, myocardial lactate extraction.
† $p < 0.05$ from preinduction.
‡ $p < 0.05$ from postinduction.

TABLE 2

Hemodynamic and Myocardial Energy Metabolic Responses in Halothane Group I*

	HR	MAP	SVR	PCW	CI	CBF	CS-O_2 content	MV_{O_2}	MLE
	beats/min	mm Hg	dynes·sec·cm^{-5}	mm Hg	L/min/m^2	ml/min	ml/dl	ml/min	%
Before induction	69 ± 2	77 ± 4	1071 ± 83	12 ± 2	2.9 ± 0.2	107 ± 18	6.0 ± 0.4	10.1 ± 2.3	26 ± 5
After induction	71 ± 3	64 ± 2	995 ± 45	11 ± 1	2.5 ± 0.1	94 ± 30	8.0 ± 0.4†	6.7 ± 2.3†	35 ± 6
After intubation	86 ± 2‡	95 ± 7‡	1217 ± 104	13 ± 1	3.1 ± 0.1	103 ± 33	7.2 ± 0.7	8.7 ± 3.0	29 ± 6
Before sternotomy	66 ± 4	78 ± 5	1176 ± 127	17 ± 2†	2.6 ± 0.2	80 ± 19	5.1 ± 0.9	6.5 ± 1.6	33 ± 3
After sternotomy	77 ± 8	79 ± 6	1181 ± 151	16 ± 1†	2.6 ± 0.2	93 ± 15	5.4 ± 0.9	8.4 ± 1.5	27 ± 5

* Values are means ± SEM; n = 6. Abbreviations are defined in Table 1 footnote.
† $p < 0.05$ from preinduction.
‡ $p < 0.05$ from all other series.

Results in halothane group II are shown in Table 3. With the morphine premedication given subcutaneously, these patients tended to have higher blood pressures and greater systemic vascular resistances before induction, than did patients who received their premedicating morphine intravenously. Subsequently, the decrease in systemic vascular resistance (25%) on induction with halothane and the 30% decrease in MAP ($p < 0.05$) were greater than in halothane group I. There was no significant change in CBF, so the 38% reduction in MV_{O_2} ($p < 0.05$) was associated with a large increase in CS oxygen content ($p < 0.05$). The autonomic stimulation of intubation significantly increased heart rate, MAP, and MV_{O_2} and decreased CS oxygen content ($p < 0.05$). Cardiac index and PCW did not vary significantly at any time. Sternotomy was well tolerated hemodynamically (no patients required nitroprusside) but was associated with an increase in MV_{O_2} and a greater CBF. Mean MLE for the group remained normal, but one patient showed myocardial lactate production after sternotomy. One patient in this group had postoperative electrocardiogram and enzyme evidence of mild infarction but recovered uneventfully.

No other patients had postoperative complications and all were discharged home. There were no complications from presence of the catheter in the coronary sinus for 24 hours after operation. Changes in ST segment configuration were not seen at any time in this study.

Discussion

Although both morphine and halothane have been used widely as major agents in anesthesia for patients with coronary disease, the myocardial metabolic cost imposed by these drugs is not well documented. The major reason has been the difficulty in measuring coronary flow in the clinical setting. Our study examined the energy metabolism of the left ventricle during anesthesia with these agents, specifically their effects on myocardial oxygen supply and demand.

In studying anesthetic agents in patients with coronary disease, patient safety dictates not only that one anesthetic drug cannot be given but also that premedication cannot be omitted. Hence our study was necessarily not pharmacologically "pure" but instead consisted of two anesthetic techniques with the major anesthetic being either morphine or halothane. The awake control measurements were made in quiet, sedated, responsive patients whose cardiovascular status was probably closer to normal than if the patients had been studied without premedication. A minimal dose of thiopental was given to initiate induction of halothane anesthesia and diazepam was given during induction of morphine anesthesia to assure amnesia. All patients received pancuronium for paralysis. We cannot rule out contributions of these medications (5, 6) to the hemodynamic and metabolic responses observed, but the majority of these responses were due predominantly to the agents (morphine and halothane) given in largest doses.

It is also important to describe the patients studied in detail, as the results obtained in one clinical setting may not apply in others. Our patients had serious coronary arterial disease but with ventricular function preserved and no other complicating factors. We presume that the state of beta-adrenergic blockade was less than complete, though 15 of the 18 patients were taking propranolol. Patients who had control PCW pressures of less than 12 mm Hg, had PCW increased to 12 mm Hg before induction by fluid infusion, to establish a more uniform base of ventricular function. The mean MV_{O_2} of the total group, 10.6 ml/min before induction, was less than the 15 ml/min found by Baller et al (7) in awake subjects with coronary disease, probably because our patients were sedated.

Circulatory Responses

The changes on induction with both halothane and morphine were similar to those previously documented (1). The percent changes throughout are evident in Fig 1. The decrease in blood pressure was

TABLE 3

Hemodynamic and Myocardial Energy Metabolic Responses in Halothane Group II*

	HR	MAP	SVR	PCW	CI	CBF	CS–O₂ content	MV_{O_2}	MLE
	beats/min	mm Hg	dynes·sec·cm⁻⁶	mm Hg	L/min/m²	ml/min	ml/dl	ml/min	%
Before Induction	68 ± 6	100 ± 6	1510 ± 109	16 ± 3	2.6 ± 0.2	115 ± 15	5.9 ± 0.4	12.0 ± 2.5	28 ± 5
After Induction	74 ± 6	70 ± 6†	1127 ± 123	14 ± 1	2.4 ± 0.2	100 ± 15	8.6 ± 0.4†	7.4 ± 1.6†	29 ± 6
After Intubation	92 ± 8‡	104 ± 7‡	1579 ± 189	16 ± 4	2.5 ± 0.1	115 ± 15	7.3 ± 0.4‡	9.8 ± 1.7	21 ± 7
Before sternotomy	74 ± 6	92 ± 9	1336 ± 142	21 ± 3	2.5 ± 0.1	91 ± 14	6.3 ± 0.5	8.3 ± 1.9	27 ± 6
After sternotomy	82 ± 9	94 ± 7	1535 ± 293	22 ± 2	2.5 ± 0.3	122 ± 17	5.7 ± 0.5	11.3 ± 2.4§	21 ± 7

* Values are means ± SEM; n = 6. Abbreviations are defined in Table 1 footnote.
† $p < 0.05$ from preinduction.
‡ $p < 0.05$ from postinduction.
§ $p < 0.05$ from presternotomy.
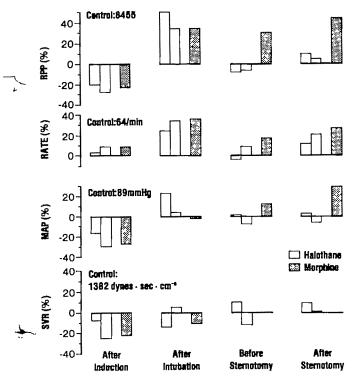
FIG 1. Percent changes in rate-pressure product (RPP), heart rate, mean arterial pressure (MAP), and systemic vascular resistance (SVR), from mean preinduction control values in three groups.

primarily due to decreased vascular resistance, as cardiac output was reduced only a small amount. The lack of change in cardiac output with halothane differs from that found by others (1). It probably reflects a lighter level of anesthesia in our patients, in spite of the hypotension. Unfortunately, we documented only inspired concentrations, up to 3% for at least 10 minutes, the maximum possible without treatment of the decrease in blood pressure.

With tracheal intubation, hemodynamic responses returned to awake level, the increase in heart rate indicating incomplete beta blockade. From that point on through the study, circulatory stability was maintained with the halothane-oxygen technique.

Clearly the 1 mg/kg of morphine did not obtund the sympathetic response to sternotomy, as both pulse rate and MAP increased. Four of the six patients had to be given a nitroprusside infusion immediately after the poststernotomy measurements were made.

However, our patients' responses to sternotomy after 1 mg/kg of morphine were the same as those reported by Kistner et al (8), following 2.1 mg/kg of morphine in patients having CABG. They found elevations of heart rate and blood pressure after sternot-

omy together with significant ST segment depression. Similarly, Wilkinson et al (9), in 12 patients receiving 2 mg/kg of morphine, found a significant number of ischemic episodes.

Coronary Flow and MV_{O_2}

The coronary sinus catheter enables measurement of coronary flow and arteriovenous difference of oxygen content, the essential components for calculating MV_{O_2}.

Limitations of this thermodilution method have been summarized (3, 10). Although differences in flow were seen from patient to patient, sequential measurements in each patient were quite consistent (3). Coronary sinus blood is almost exclusively that from the left ventricular muscle (11). In patients having cardiac catheterization, Ganz et al (3) found mean CBF to be 128 ± 20 (SD) ml/min. Sonntag et al (12) reported left coronary flow, as measured by the argon method, to be 88 ml/100 g/min or 132 ml/min for a normal left ventricle. Mean CBF in our 18 patients before induction of anesthesia was 110 ± 13 (SD) ml/min. With our measurements in close agreement, we believe our method was accurate.

The trends of change in coronary flow and energy metabolism, as percent changes from the awake state, are shown in Fig 2. In spite of the decrease in perfusing pressure, significant decreases in CBF did not occur on induction with either morphine or halothane. Nor did CBF increase above the awake level upon development of a hyperdynamic state after sternotomy.

The striking reduction in MV_{O_2} on induction with both the agents we studied was almost entirely due to decreased oxygen extraction (i.e., narrowing of the arteriovenous difference in oxygen content) rather than to decreases in CBF, which did not change. The oxygen saturation of coronary sinus blood almost doubled after induction, before intubation. The myocardium extracted far less of the oxygen presented to it, as myocardial work decreased. On intubation, MV_{O_2} promptly returned toward the awake level, but even with subsequent surgical stimulation, MV_{O_2} did not exceed that observed in the awake state. Reduced body temperature was probably a factor in the rate of oxygen consumption.

Myocardial Lactate

In the presence of sufficient oxygen, the myocardium extracts more than 20% of coronary arterial lactate to produce adenosine triphosphate (ATP). A concentration of lactate that is higher in coronary
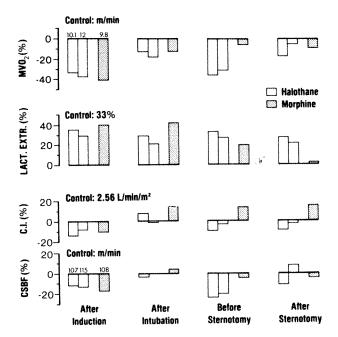
FIG 2. Percent changes in myocardial oxygen consumption (MV$_{O_2}$), lactate extraction (lact extr), cardiac index (CI), and coronary sinus blood flow (CSBF), from mean preinduction control values in three groups.

sinus blood than in coronary arterial blood is evidence of global anaerobic glycolysis of the myocardium. We found lactate production after sternotomy in two of six patients given morphine and in one of 12 patients receiving halothane. Clearly, if the sympathetic response to surgical stimulation is not obtunded in patients with coronary disease, myocardial oxygen consumption will exceed supply.

We emphasize that our study examined myocardial oxygenation only globally. The coronary sinus pool contains blood from all sections of the left ventricle. Evidence of ischemia in local areas poorly supplied with oxygen may be completely hidden in the larger pool of blood from nonischemic muscle. As yet there are no data on regional oxygen balance under the conditions of our study. However, when the sinus blood contains more lactate than that entering the coronary arteries, ischemia of a large proportion of the ventricle must be present.

Evidence of Myocardial Ischemia

There were no changes in ST segments or other electrocardiogram evidence of ischemia at any time in any patient. This was also the case in patients who had myocardial lactate production and in patients

with rate-pressure products up to 16,000. This differs from the finding of Wilkinson et al (9) who studied CABG patients given morphine or halothane, using the same method of coronary sinus flow measurement. They saw a significant number of ischemic episodes as evidenced by ST changes and lactate production with both agents. The only discernible difference in anesthetic technique between their study and ours was that nitrous oxide was part of their technique and not of ours. Absence of ST changes seems not be an assurance of adequate oxygenation and rate-pressure products seem at best to be imprecise indices of myocardial oxygen balance.

In summary, in 18 patients having CABG, we found that MV$_{O_2}$ decreased more than oxygen supply on induction of anesthesia with either halothane or morphine. There was no evidence of global myocardial ischemia. Maintenance of anesthesia with halothane-oxygen resulted in hemodynamic stability and preservation of oxygen balance. Morphine-oxygen, 1 mg/ kg, did not adequately control the sympathetic response to sternotomy, with myocardial oxygen consumption exceeding supply in some patients. Neither changes in ST segments nor the rate-pressure product were useful aids in indicating episodes of myocardial ischemia.

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Brachial Plexus Block for Pain Relief after Modified Radical Mastectomy

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FASSOULAKI, A.: Brachial plexus block for pain relief after modified radical mastectomy. Anesth Analg 1982;61:986–7.

Brachial plexus block using an infraclavicular approach was performed at the completion of surgery in 47 patients having modified radical mastectomies. In 48 control patients having similar operations, brachial plexus block was not performed. Of the 47 patients in whom brachial plexus block was performed, 26 (55%) required analgesia during the first 24 hours after the operation, whereas 44 (91%) of the 48 control patients required analgesics ($p < 0.0005$). The time elapsed between the end of anesthesia and requirement of the first analgesic was significantly longer when the brachial plexus was blocked ($p < 0.001$). The efficacy, simplicity, and safety of blocking the brachial plexus at the completion of surgery following modified mastectomy demonstrate that this technique could be routinely used for the relief of postoperative pain in patients having modified radical mastectomies.

Key Words: PAIN: postoperative, mastectomy; ANESTHETIC TECHNIQUES: infraclavicular plexus block.

REGIONAL ANALGESIA has been used to reduce postoperative pain. Intercostal nerve blocks after thoracotomy (1) and posterior intercostal blocks for pain relief after cholecystectomy (2, 3) are classic examples. Modified radical mastectomy produces pain in the axilla and the upper limb. The present study has explored the use of brachial plexus block by an infraclavicular approach for control of pain after modified radical mastectomy.

Methods

Ninety-five female patients undergoing modified radical mastectomy (removal of the breast and dissection of the axillary lymph nodes) were studied. Each patient was seen by the anesthesiologist the night before the operation and consent to participate in the trial was obtained. The anesthetic procedure was similar for all patients. Premedication consisted of diazepam, 20 mg, given orally 90 minutes before induction of anesthesia. Anesthesia was induced with thiopental, 5 mg/kg body weight, and fentanyl, 3 μg/kg, followed by suxamethonium to facilitate tracheal intubation, and was maintained with halothane 0.5%

and 66% nitrous oxide in oxygen. Respiration was controlled and pancuronium was given as required.

Patients were randomly allocated to one of two groups: those who had the brachial plexus on the operative side blocked using bupivacaine 0.5% with epinephrine 1:200,000 (47 patients), and those who did not have a brachial plexus block (48 patients). The block was performed by the surgeon at the infraclavicular part of the brachial plexus after completion of surgery before closure of the incision. The volume of bupivacaine used was 15 ml. After removal of the mammary gland, the intercostal spaces underneath the skin incision were also infiltrated with 5 ml of bupivacaine. The remaining 48 patients who did not receive any sort of regional analgesia made up the control group.

Postoperative analgesics were given as required and nurses in the recovery room and later in the ward recorded the time at which they were administered. The nurses had no knowledge of the treatment, if any, that had been given. Pain was assessed for 24 hours following surgery.

Statistical analysis of the results was performed using chi-square test for nonparametric data and Student's t-test for parametric data.

Results

Of the 47 patients in whom brachial plexus block was performed, 26 (55%) required analgesia in the

first 24 postoperative hours. Of the 48 control patients, 44 (91%) needed analgesics in the same time. Brachial plexus block with bupivacaine significantly reduced the number of patients needing analgesics in the first 24 hours following surgery (chi square = 16.19, $p < 0.0005$). The mean time elapsed between the end of anesthesia and the time when the first analgesic was needed was significantly prolonged in patients having brachial block, 467 ± 53.47 (SEM) minutes compared with 100 ± 13.55 (SEM) minutes in the control group (t = 6.64 and $p < 0.001$).

Discussion

Pain is a subjective experience and no objective method exists by which postoperative pain can be precisely estimated. In the present study, postoperative pain was quantified by means of the analgesic requirements after operation and the time between the end of anesthesia and the time when a postoperative analgesic was first required.

Patients having modified radical mastectomies frequently complain of pain in the axilla and the upper limb. In view of the advantages claimed for the use of regional analgesia for management of pain in the immediate postoperative period following other types of surgery, we felt brachial plexus block might be advantageous to patients having mastectomies. No similar report is available in the literature. The results are more than encouraging. The number of patients requiring analgesics in the first 24 hours after surgery was significantly reduced, whereas the time elapsed from the end of anesthesia to the administration of the first analgesic was significantly increased. The reader might consider that part of the analgesia may have resulted from immobility as movement induces pain and brachial plexus block reduces or eliminates voluntary motor movement. However, in a few patients I have deliberately abducted the arm after performing the brachial plexus block in the recovery room. No pain was elicited. No patient had systemic side effects associated with the bupivacaine used for the blocks. Maximum plasma levels of 2.0 μg/ml of bupivacaine 25 minutes following 30 ml of bupivacaine (a dose twice the amount we used) have been reported, a level far below toxic levels (4.0 μg/ml) (4). As the dose of the local anesthetic used in the present study was lower, plasma levels of bupivacaine would be expected to be lower as well. The addition of

epinephrine results in even lower concentrations (5). Possible early signs of toxicity of bupivacaine might, of course, have been obscured by general anesthesia. This seems unlikely as in our studies infiltration of the plexus was done before skin closing, but meticulous aspiration is imperative to avoid the intravascular injection of the local anesthetic.

Bupivacaine is the local anesthetic agent of choice as the duration of analgesia following regional block with this drug is longer than when other local anesthetics are used (6). A possible prolonged time of onset is not of importance as the analgesic effect is desirable after surgery, not for the surgical procedure itself.

In our study the surgeon could infiltrate the brachial plexus under direct vision using an infraclavicular approach, a far more effective technique than an axillary or an interscalene block. As the plexus is exposed when infiltrated directly there is no danger of pleural puncture. Other advantages of the technique are the prolonged period of postoperative analgesia and the reduced requirement for potent analgesic drugs. Patients hypersensitive to the local anesthetic or those who will not accept intraoperative brachial plexus block are the only patients in whom this technique would be contraindicated. The technique described might find widespread application for the postoperative relief of pain in patients having modified radical mastectomies.

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A Double-Blind Comparison of Cimetidine and Ranitidine as Prophylaxis against Gastric Aspiration Syndrome

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Preoperative cimetidine, ranitidine, or placebo were administered, orally or intravenously, to 190 patients in a double-blind study. The volume and pH of gastric aspirate samples, obtained after tracheal intubation and before extubation, were measured. Both cimetidine and ranitidine produced higher mean pH levels and thus fewer patients "at risk" should gastric aspiration occur (pH $\leq$ 2.5) than did placebo. Intravenous ranitidine (in both 40- and 80-mg doses) produced fewer patients at risk in the event gastric aspiration should occur than did cimetidine, 300 mg, and the 80-mg dose produced a higher mean pH level. Oral ranitidine, 150 mg, produced a significantly higher mean pH level than did oral cimetidine, 300 mg, and tended to give fewer patients at risk. The volumes of gastric contents aspirated were similar following each of the drugs except that the volume was significantly less two hours following oral ranitidine, 150 mg, than after oral cimetidine, 300 mg.

Key Words: GASTROINTESTINAL TRACT: stomach, cimetidine, ranitidine.

RANITIDINE (1) is a new highly selective H_2 receptor antagonist and would appear to be more potent than cimetidine, the only currently available H_2 receptor antagonist (2) approved for clinical use. Preoperatively administered cimetidine is partially effective in increasing the pH of gastric juice to greater than 2.5, the critical level generally accepted as protecting against the adverse effects of gastric aspiration syndrome (3). However, some patients are still found to have a gastric pH of 2.5 or less after cimetidine and thus be potentially at risk for gastric aspiration syndrome (4, 5). The present double-blind study was designed to compare the effect of cimetidine, ranitidine, or placebo when administered before surgery by the oral or intravenous route, on the pH and volume of gastric aspirate at the time of intubation and extubation.

Methods

Institutional approval of the protocol was obtained

and all patients gave written informed consent before entry into the study. Patients studied were A.S.A. class I or II, aged 16 to 70 years, weighed between 40 to 90 kg, and were undergoing elective surgery that required tracheal intubation. Patients were excluded from the study if they had gastric, duodenal, esophageal, renal, or hepatic disease, and were receiving drugs that may affect gastric pH or volume, or were pregnant or nursing. The study was conducted in two segments, according to the route of administration of medication.

Intravenous Administration

One hundred patients were randomly assigned, within blocks of four, to receive either cimetidine, 300 mg; ranitidine, 40 mg; ranitidine, 80 mg; or placebo administered intravenously 1 hour before surgery. The drugs were diluted in 10 to 20 ml of 3.3% dextrose in 0.3% saline and administered via a previously established intravenous cannula over a period of 2 minutes.

Oral Administration

Ninety patients were randomly assigned, within

blocks of six, to receive either cimetidine, 300 mg; ranitidine, 150 mg; or placebo administered orally, 2 or 4 hours before the estimated time of surgery.

All patients fasted for a minimum of 6 hours before surgery. Oral diazepam was administered 2 hours before surgery when premedication was considered desirable. To ensure blinding, all study medications were administered by a nurse not involved in the anesthesia or gastric sampling.

Immediately after tracheal intubation a #16 French gauge Salem gastric tube was inserted. The gastric contents were aspirated at that time and also before extubation. Both volumes were recorded and the pH

of each sample was measured using a Fisher Accumet 320 pH meter. Patients in whom the pH of gastric juice was 2.5 or less were considered to be at risk of severe pulmonary reaction in the event that gastric aspiration should occur. Side effects were evaluated by direct questioning of the patient immediately before anesthesia. The duration of fasting and the times from administration of the test drug to both intubation and extubation were recorded.

Numerical data were analyzed using the independent t-test. Ordinal data were compared using a Fisher exact or chi-square test as appropriate. A level of $p \leq 0.05$ was considered to be statistically significant.

Results

In both segments of the study, treatment subgroups were similar with respect to age, weight, and height (Tables 1 and 2). The duration of fasting was similar in all subgroups. In some patients, a sample of gastric juice could not be obtained after intubation or before extubation. In 15 patients in the intravenous administration group, an intubation sample was unobtainable. Accordingly, these patients were not included in the results in Table 3. One patient in the oral admin-

TABLE 1
Patients Receiving Intravenous Medications*

	n	Age	Weight	Height
		yr	kg	cm
Cimetidine, 300 mg	25	36.8 ± 2.70	62.2 ± 2.19	163.1 ± 1.66
Ranitidine, 40 mg	25	37.7 ± 3.52	65.4 ± 2.81	166.9 ± 2.34
Ranitidine, 80 mg	26	41.7 ± 2.89	70.3 ± 2.84	166.8 ± 1.85
Placebo	25	44.0 ± 2.86	68.6 ± 3.18	165.2 ± 2.10

* Values are means ± SEM for patients receiving study medications by the intravenous route.

TABLE 2
Patients Receiving Oral Medications*

	n	Age	Weight	Height
		yr	kg	cm
2 hr				
Cimetidine	16	37.9 ± 3.89	71.5 ± 4.04	169.2 ± 2.36
Ranitidine	16	43.7 ± 3.16	66.2 ± 2.83	163.4 ± 1.74
Placebo	16	41.4 ± 3.94	67.3 ± 2.48	165.5 ± 2.48
4 hr				
Cimetidine	14	34.5 ± 3.39	66.6 ± 3.40	166.6 ± 2.05
Ranitidine	14	38.9 ± 3.97	71.2 ± 3.73	169.6 ± 2.09
Placebo	14	34.0 ± 3.56	68.2 ± 4.41	166.3 ± 3.57

* Values are means ± SEM for patients receiving study medications by the oral route.

TABLE 3
Findings at Time of Intubation after Intravenous Medication*

	n	Time from medication to sampling	Volume of gastric aspirate	Gastric pH	No. at risk
		min	ml		
Cimetidine, 300 mg	20	76.9 ± 9.83	12.1 ± 1.88	5.0 ± 0.53‡	7 (35%)
Ranitidine, 40 mg	21	76.3 ± 5.10	15.1 ± 3.58	5.1 ± 0.44‡	4 (19%)
Ranitidine, 80 mg	20	64.0 ± 4.18	15.6 ± 3.72	5.8 ± 0.41‡	1† (5%)
Placebo	24	75.2 ± 5.50	19.5 ± 4.07	2.2 ± 0.23	20 (83%)

* Values are means ± SEM. Patients at risk are those with a gastric pH ≤ 2.5.
† $p < 0.05$ when compared with cimetidine.
‡ $p < 0.0001$ when compared with placebo.

istration group, in whom a gastric tube could not be passed, was replaced in the study, and in eight other patients a gastric juice sample was unobtainable at intubation.

Intravenous Group

The mean values, at intubation, for the time between intravenous drug administration and sampling, for pH and volume of gastric aspirate, and for the number of patients at risk with each medication dose are summarized in Table 3.

There were no statistically significant differences between medications in the time intervals from drug administration or for aspirated volumes. Mean pH values following cimetidine and both ranitidine doses were similar and all were significantly higher than placebo ($p < 0.001$). However, there was a significant difference between cimetidine and ranitidine, 80 mg, when comparing the number of patients at risk ($p = 0.045$). The results at extubation were similar to those at intubation except that volumes of gastric aspirate tended to be smaller.

The incidence of side effects was as follows with the intravenous medications: mild headache occurred in one of the patients given cimetidine, in two patients given each of the ranitidine doses, and in three patients given the placebo injections. In some patients, mild itching occurred at the intravenous site during administration of the test drug. The incidence was: cimetidine, one: ranitidine, 40 mg, two; ranitidine, 80 mg, three; placebo, zero. One patient receiving ranitidine, 80 mg, developed severe itching and redness in the arm in which the drug was being infused, causing the administration to be terminated before all of the drug was given. This cleared up without further problems and this patient was replaced in the study.

Oral Group

The mean values at intubation for the time between oral drug administration and sampling, for pH and volume of gastric aspirate, and for the number of patients at risk with each medication are summarized in Table 4. The 2- and 4-hour administrations are presented as different subgroups.

In each of the medication doses in the 2- and 4-hour subgroups, the mean intervals between drug administration and sampling were similar. The aspirated volumes were similar for medications in the 4-hour subgroup, but, in the 2-hour subgroup, the volume following ranitidine was less than that for cimetidine and placebo ($p = 0.008$ and 0.04, respectively). Mean pH value following placebo was significantly lower than that after both cimetidine and ranitidine at both time administrations ($p < 0.001$). The mean pH value after ranitidine was significantly higher than after cimetidine in both the 2- and 4-hour subgroups at the time of intubation ($p < 0.01$). The results at extubation were again similar to those at intubation except that volumes of gastric aspirate tended to be smaller, and the pH after ranitidine was higher than that following cimetidine although the difference was not statistically significant. The number of patients at risk did not differ significantly between cimetidine and ranitidine but was less than with placebo.

The distribution of gastric aspirate pH values as a function of the time interval between administration of cimetidine or ranitidine and intubation sampling is shown in the Figure. Two of the three patients at risk following ranitidine received the drug less than 2 hours before intubation. Following cimetidine, six patients who received the drug 2 to 3 hours before intubation sampling were at risk.

TABLE 4

Findings at Time of Intubation after Oral Medication*

	n	Time from medication to sampling	Volume of gastric aspirate	Gastric pH	No. at risk	
		min	*ml*			
2 hr						
Cimetidine, 300 mg	14	137.0 ± 2.19	15.9 ± 2.88	4.0 ± 0.53‡	4	(29%)
Ranitidine, 150 mg	13	136.3 ± 9.10	6.8 ± 1.07†	6.1 ± 0.53†‡	2	(15%)
Placebo	15	138.3 ± 8.33	20.0 ± 5.55	2.3 ± 0.34	13	(87%)
4 hr						
Cimetidine, 300 mg	12	220.7 ± 17.52	11.8 ± 2.99	3.9 ± 0.54†	4	(33%)
Ranitidine, 150 mg	14	216.8 ± 23.54	9.8 ± 2.22	5.8 ± 0.46†‡	1	(7%)
Placebo	14	203.3 ± 14.56	15.2 ± 3.10	1.9 ± 0.08	14	(100%)

* Values are means ± SEM. Patients at risk are those with a gastric pH ≤ 2.5.
† $p < 0.01$ when compared with cimetidine, 300 mg.
‡ $p < 0.001$ when compared with placebo.
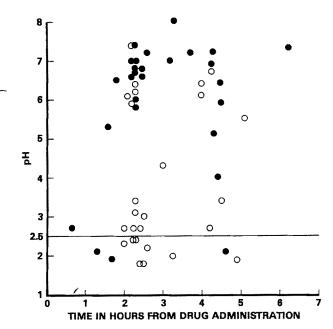
FIGURE. pH of gastric aspirate at time of intubation following oral administration of cimetidine, 300 mg (O), or ranitidine, 150 mg (●), as function of time from drug administration.

The incidence of side effects was low following the oral medications. Two patients who received cimetidine and two who received ranitidine developed mild headaches with nausea. No side effects were seen following orally administered placebo.

Discussion

Gastric acid aspiration syndrome continues to be a significant risk in anesthesia (6–8). A number of agents, including cimetidine, have been investigated in the hope that preoperative administration will consistently result in a gastric pH greater than 2.5 at the time of intubation. However, preoperative cimetidine does not consistently increase gastric pH to greater than 2.5 and the percentage of patients at risk varies from 10% following 300 mg of cimetidine given intravenously (4) to 16% when given orally (5). Ranitidine, a new H_2 receptor antagonist that is more selective, potent, and longer acting than cimetidine was therefore studied to determine whether it would be more effective than cimetidine in increasing gastric pH.

In addition to a gastric pH level of 2.5 or less, a minimum gastric volume of 25 ml is often used to define patients at risk of severe pulmonary reaction in the event that gastric acid aspiration should occur (3). However, in this study it was decided to define risk solely on the basis of the pH level, as it was not considered that the method of gastric aspiration ensured an accurate measure of the total gastric contents.

Both cimetidine and ranitidine, when compared with placebo, resulted in significantly higher gastric pH levels and fewer patients at risk in the event that gastric aspiration should occur. In terms of producing the fewest patients at risk, ranitidine, 80 mg, administered intravenously was the most effective dose regimen. Oral ranitidine, 150 mg, given 4 hours before surgery was as effective as 80 mg given intravenously in increasing gastric pH and only one patient in 14 had a gastric pH ≤ 2.5. A similar result has recently been reported in a study (9) in which ranitidine, 150 mg, was administered orally on the evening before as well as on the morning of surgery. In this study, two of the three patients at risk after oral ranitidine received the drug less than 2 hours before intubation, whereas the one other patient at risk received the drug more than 4 hours before intubation; therefore a time interval of more than 2 hours from drug administration does not seem to ensure that gastric pH will be in a safe range.

The duration of action of ranitidine is reported to be longer than cimetidine, but in this study gastric pH at the time of extubation did not decrease to less than levels observed at the time of intubation even in patients studied up to 7 hours after the oral administration of cimetidine or ranitidine. In fact, the pH value in all groups including placebo tended to be slightly higher at extubation than at intubation, confirming a previous report that the gastric pH tends to increase during anesthesia and surgery (10).

The incidence of side effects was low and consisted mainly of itching at the site of intravenous administration of cimetidine and ranitidine. The incidence following ranitidine tended to be higher but this was not a statistically significant difference from that following cimetidine. One patient, receiving ranitidine, 80 mg, intravenously, had a severe local reaction at the site of injection necessitating cessation of drug infusion. Thus, for 80 mg of ranitidine, perhaps further dilution or a slower intravenous administration should be considered.

Ranitidine is at least 4 times as potent as cimetidine on a molar basis (1, 11), and therefore the doses of cimetidine and ranitidine studied may not be equipotent. However, 300 mg of cimetidine is the recommended dose (2), and it has been used in other studies (4, 5). Oral ranitidine, 150 mg, is the dose that has been studied, but this may be more potent than the dose of cimetidine used. Intravenous ranitidine, 80 or 40 mg, is approximately ¼ to ⅛ the 300-mg dose of cimetidine studied, and therefore may be considered to be in the equipotent range.

In conclusion, both cimetidine and ranitidine were significantly better than placebo in producing a higher mean pH and fewer patients at risk in both the oral and intravenous administration groups. Ranitidine, 80 mg, administered intravenously produced both a higher mean pH and thus fewer patients at risk than did cimetidine 300 mg. Ranitidine, 40 mg, administered intravenously also resulted in fewer patients at risk than did cimetidine, 300 mg. Mean gastric pH levels were similar after both doses of intravenous ranitidine. Oral ranitidine was associated with significantly higher pH values than oral cimetidine and thus also tended to decrease the number of patients at risk. In view of the lack of side effects following oral ranitidine, this would appear to be the preferred route of administration, when clinically appropriate, for protection against gastric aspiration syndrome.

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Continuous Intravenous Anesthesia with Etomidate for Carbon Dioxide Laser Surgery of the Larynx

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SIA, R. L., ZANDSTRA, D. F., AND VAN OVERBEEK, J. J. M.: Continuous intravenous anesthesia with etomidate for carbon dioxide laser surgery of the larynx. Anesth Analg 1982;61:993-6.

Twenty-five adult patients undergoing carbon dioxide laser surgery for benign and malignant disease of the larynx were given continuous infusion of etomidate at 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for induction of anesthesia. Maintenance anesthesia was continued using one of three infusion rates: 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n = 5), 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n = 10), and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n = 10) of etomidate in air-oxygen mixture. Muscular relaxation was achieved by continuous infusion of succinylcholine, and fentanyl was used for analgesia. Continuous etomidate infusion for induction of anesthesia resulted in a significant decrease in the incidence of pain along the injection site to 8% and involuntary muscular movements to 12% compared with 36% and 44%, respectively, in a group of 25 adult patients undergoing endoscopic procedure who received intravenously a single bolus injection of etomidate (0.3 mg·kg^{-1}). However, a prolonged recovery time was observed after 30 minutes of continuous etomidate infusion.

Key Words: ANESTHETICS, intravenous: etomidate; ANESTHESIA: otolaryngologic.

SINCE THE introduction of carbon dioxide laser surgery for the treatment of benign and malignant pathology of the vocal cords and larynx, one of the most widely used anesthetic techniques consists of thiopental for induction of anesthesia followed by succinylcholine for tracheal intubation with maintenance of anesthesia using nitrous oxide–oxygen and halothane or enflurane plus d-tubocurarine, pancuronium, or succinylcholine infusion for muscular relaxation (1–3).

Etomidate, a nonbarbiturate, has the advantages of ultrashort duration of action (4, 5), little cumulative effect, absence of histamine release (6), and cardiovascular stability (7, 8) when used as bolus injection during induction of anesthesia. For these reasons we evaluated the use of continuous infusion of etomidate during CO_2 laser surgery of the larynx using three dosages to determine the effect on recovery time, the frequency of pain at the infusion site, and the frequency of involuntary muscle movements during induction and maintenance of anesthesia.

Patients and Methods

Twenty-five adult A.S.A. class I or II patients admitted for elective CO_2 laser treatment of benign and malignant conditions of the vocal cords and larynx gave informed consent for this study. Patients' ages ranged between 17 to 56 years (mean 34) and weight between 50 to 76 kg (mean 60).

Premedication consisted of papaveratum, 10 mg, and atropine, 0.5 mg, 1 hour before the operation. Anesthesia was induced using an etomidate infusion delivered by an IVAC (IVAC 531, IVAC Corp., San Diego, CA) pump (250 mg of etomidate in 250 ml of glucose-NaCl using the 125-mg ampule containing alcohol solvent) at a rate of 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in all patients for approximately 5 minutes until consciousness and the eyelid reflex were lost. Following oxygenation by face mask, succinylcholine, 1 mg·kg^{-1}, was administered and tracheal intubation was performed. Maintenance of anesthesia was by continuous intravenous infusion of etomidate at one of three rates: 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n = 5), 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n = 10), and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n = 10). Fentanyl, 0.1 mg, was administered intravenously after tracheal intubation and an additional dose of 0.05 to 0.1 mg was given if the patient reacted during the procedure or when the procedure lasted more than 30 minutes. Relaxation of the laryngeal musculature during surgery was achieved using a 1% succinylcholine infusion

at 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$; if the vocal cords began to contract the infusion rate was increased to 75 to 90 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Patients were ventilated using an air-oxygen mixture (6:1 L/min) at a frequency of 16 breaths per minute using an Engström ventilator. The etomidate and suxamethonium infusions were discontinued at the end of the laser procedure and the patients were then manually ventilated using oxygen. The duration of anesthesia varied from 16 to 62 minutes. Blood pressure and electrocardiogram were monitored during anesthesia. Precautionary measures to avoid possible burns during use of CO_2 laser included aluminum wrapping around the armored tracheal tubes.

In 25 adult patients (similar premedication) undergoing short endoscopic procedures for esophagoscopy and direct laryngoscopy anesthesia was induced with a single bolus dose of etomidate, 0.3 $mg \cdot kg^{-1}$, intravenously. After face mask oxygenation, succinylcholine, 1 $mg \cdot kg^{-1}$, was administered to facilitate tracheal intubation, and maintenance anesthesia was with 0.5% to 1% halothane, 67% nitrous oxide in oxygen. No fentanyl was administered before the induction of anesthesia.

During etomidate infusion or bolus etomidate administration, the patient was asked a standard question: "What do you feel in your arm?" Pain was recorded as Yes/No; slight discomfort was recorded as No.

Recovery time (minutes) was measured as the time from the cessation of the etomidate infusion until the patient opened his eyes and responded to verbal commands evaluated every 5 minutes. The mean induction time, mean induction dose of etomidate, mean fentanyl dose, and mean duration of anesthesia were calculated. Results are expressed as means ± SD. Regression analysis of the recovery time with the three infusion rates and total etomidate dose were also calculated.

Results
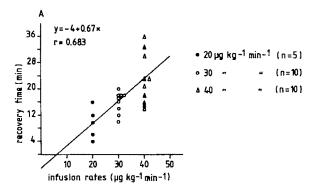
The mean duration of anesthesia for the three etomidate dosage regimes were: 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 20 ± 4 minutes; 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 29.7 ± 7.5 minutes; and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 39 ± 16 minutes. The mean induction time was 4.62 ± 0.79, minutes mean induction dose of etomidate was 17.96 ± 3.49 mg, and mean fentanyl dose was 0.18 ± 0.04 mg. Regression analysis of the recovery time with the three infusion rates and total etomidate dose for each patient showed prolonged recovery time and gave significant correlations with coefficients of 0.683 and 0.928, respectively.

tively (Figure). The mean recovery times for the three etomidate dosage regimes were 9.6 ± 4.8, 15.9 ± 3.1, and 22.9 ± 7.8 minutes, respectively. The mean total induction dose of etomidate and mean recovery time in the single bolus dose group of patients were 13.20 ± 7.36 mg and 2.74 ± 0.72 minutes, respectively.

Pain on injection and involuntary muscle movements were significantly reduced to 8% and 12%, respectively, compared with 36% and 44%, respectively, with the single bolus dose induction. Muscular movements due to minor surgical stimulation in 40% of patients were observed when the infusion rate was 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$, but were not encountered with the two higher infusion rates. During suspension laryngoscopy and tracheal manipulation, episodes of tachycardia, bradycardia, and extrasystoles were observed from time to time, but blood pressure and heart rate in general remained remarkably stable during the course of anesthesia.

Discussion

In CO_2 laser treatment of the vocal cords and larynx, several points of cardinal importance should be considered when using a continuous etomidate intravenous anesthesia technique: (a) as the airway is
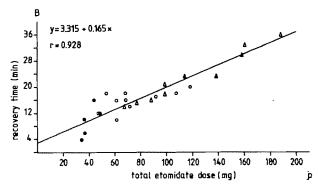
FIGURE. Regression analysis of recovery time with infusion rates and total etomidate dose for each patient. Both show significant linear correlation with coefficient 0.683 and 0.928, respectively.

involved in the procedure, early recovery from anesthesia and neuromuscular blockade should be of primary concern and importance. (b) the drug must be safe, effective, and provide adequate levels of anesthesia: and (c) operating room pollution, as when volatile anesthetics in nitrous oxide–oxygen are used, can be avoided, along with the potential health hazard (9) associated with such pollution.

The high incidence of pain on injection and involuntary muscle movements commonly seen during etomidate bolus induction (10) were significantly reduced with the continuous etomidate infusion induction. Prior administration of fentanyl or injection of fentanyl via rapidly running infusion in order to diminish pain and involuntary muscle movements was not necessary during continuous etomidate induction infusion. Fentanyl was administered only when the patient was asleep. It appears that drug dilution, slow rate of administration, and a stable venous dose concentration are important factors in minimizing these side effects.

Recovery time appears to be influenced by the additive effects of etomidate induction dose, etomidate infusion rates, duration of anesthesia, and the amount of analgesia administered. The high plasma etomidate concentration after induction by infusion of etomidate would be expected to decrease rapidly because of tissue redistribution and metabolism. However, the subsequent maintenance infusion rates will provide variable plasma etomidate concentrations which are related to the depth of anesthesia. It appears that with the 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rates, plasma etomidate concentrations are above the awakening threshold (etomidate plasma concentration 0.2 $\mu g/ml$) and these infusion rates were found sufficient to maintain adequate hypnosis during ventilation with air-oxygen. With the 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate, the depth of anesthesia may be near the awakening threshold with consequent risk of awareness during surgical stimulation. The cumulative tendency resulting in a prolonged recovery time after continuous etomidate infusion for 1 hour could be explained on the basis that steady-state plasma etomidate concentrations are only attained after 3 to 4 times the elimination half-life of approximately 200 minutes as reported by De Ruiter et al (11).

Due to wide variations in the duration of operations (from 15 to 60 minutes), the choice of the ideal muscle relaxant can be a problem. It is our experience that during laser surgery of the larynx, the usual dose requirement (e.g., pancuronium, 0.1 $mg \cdot kg^{-1}$) which gives adequate relaxation for abdominal procedures

is not sufficient to provide complete relaxation of the vocal cords. Usually 1 ½ to 2 times the usual dose is needed to achieve profound relaxation of the vocal cords. This is essential because any slight movement of the vocal cords can lead to burning of normal tissue. It has been shown that the musculature of the vocal cords has a unique type of innervation which might explain the resistance of the laryngeal musculature to the action of non-depolarizing agents (12), but not to the depolarizing agent succinylcholine (R. L. Sia, unpublished observations, 1980). The total amount of succinylcholine used in any 1-hour procedure did not exceed 500 mg and the analgesia (fentanyl) requirement in this rather painless operation was small. Return of spontaneous breathing was usually observed shortly after stopping the succinylcholine infusion.

This study showed that prolonged continuous etomidate infusion in air-oxygen is associated with prolonged recovery time. It appears that in operations lasting more than 30 minutes, etomidate can be best used as single bolus dose injection for induction of anesthesia followed by halothane or enflurane in nitrous oxide-oxygen for maintenance of anesthesia.

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Methohexital Anesthesia in the Surgical Treatment of Uncontrollable Epilepsy

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FORD, E. W., MORRELL, F., AND WHISLER, W. W.: Methohexital anesthesia in the surgical treatment of uncontrollable epilepsy. Anesth Analg 1982;61:997-1001.

Twenty-five patients (aged 3 to 39 years) were anesthetized with methohexital for electrocorticographic mapping and resection of epileptogenic foci. These patients have been compared with 11 patients (aged 11 to 40 years) who had the same surgical procedure performed while they were awake because their epileptogenic foci were near the speech or motor areas. All patients received morphine and droperidol to produce analgesia and sedation, and a field block was established with local anesthetics. In the 25 patients, general anesthesia was induced with methohexital, 1.5 mg/kg, and maintained with a 0.1% infusion. After intubation, ventilation to a Pa_{CO_2} of 30 mm Hg was maintained with O_2/air. A resectable abnormal electroencephalogram focus was localized in every case. All but two of the patients awoke promptly in the operating room, allowing extubation and participation in neurologic assessment. None remembered the procedure. The incidence of improvement of seizures in patients given methohexital was similar to that in patients who had surgery while awake. Unlike many general anesthetics that depress epileptogenic activity, methohexital activates seizure activity and can therefore be used for the dual purpose of producing general anesthesia and enhancing electrocorticographic delineation of epileptogenic foci.

Key Words: ANESTHESIA: intravenous, methohexital; ANESTHETICS, Intravenous:methohexital; ANESTHESIA: neurosurgical, epilepsy.

SURGICAL treatment of the epilepsies, first described and performed by Foerster and Penfield in 1930 (1), has proven to be a successful mode of therapy in selected cases of uncontrollable epilepsy, but precise delineation of the epileptogenic focus by the use of intraoperative electrocorticography is essential to this success (2). Because most general anesthetics are associated with marked and prolonged suppression of epileptogenic foci (2), this surgery is usually performed with the patients awake (3). When general anesthesia has been used, the patients have been awakened intraoperatively so that recordings of interictal activity were not suppressed. It would, however, seem worthwhile to offer the benefits of general anesthesia if this were consistent with successful recording. Certain hazards of awake operation could be avoided and the disadvantages of intraoperative awakening of the patient (3) would be circumvented. Furthermore, hyperventilation, a potent activator of epileptogenic foci, could be used. We describe such a technique.

Reports that methohexital, an ultrashort-acting barbiturate, activates interictal electroencephalographic evidence of epileptic foci (4) suggested that it might be used both as a general anesthetic and to enhance electrocorticographic mapping. We now report its use in 25 focal cortical resections. Eleven patients who had foci delineated awake because of proximity to motor or speech areas served as a comparison group. This is not a proper control group as the patients were selected on the basis of different criteria. Nevertheless, the results in this group can be used to obtain a general evaluation of our success using more traditional techniques.

Methods

This series includes the 36 selective cortical resections performed in 33 patients in our hospital since 1976. Twenty-five patients (aged 3 to 40 years, mean

19.9 years) received general anesthesia using methohexital. Eleven patients (aged 11 to 40 years, mean 23.1 years) required identification of areas bordering on the focus to be resected and were operated on awake. These two groups include three patients each of whom underwent two operations.

Anesthetic Technique

All patients had their antiepilepsy medications discontinued before surgery, and paraldehyde was used as necessary for control of seizures. Premedication consisted of morphine, hydroxyzine, and an antisialogogue, alone or in combination. Barbiturates and diazepam were not used. Monitors included Doppler blood pressure probe and cuff, precordial stethoscope, Foley catheter, electrocardiogram, and temperature probe. In addition, the patients operated on under local anesthesia had a radial intra-arterial cannula inserted. In this "awake" group, increments of intravenous morphine and droperidol were given to achieve a cooperative but sedated patient with a Pa_{CO_2} level less than 48 mm Hg. Morphine was chosen over fentanyl as it was felt to offer a somewhat smoother level of analgesia and sedation. In a few later cases, fentanyl was used. The pin head-holder was placed using a mixture of lidocaine 0.5% and bupivacaine 0.375% with epinephrine 1:200,000 as local anesthetic. The same solution was used to infiltrate the incision line both superficially and deeply (above and below the galea) to the level of the periosteum. A generous amount was also infiltrated along the superior border of the zygoma and into temporalis muscle. The area where the scale flap would hinge was also infiltrated. A maximum of 1 ml/kg was used. Approximately 10 minutes elapsed before incision. If frank seizures were encountered in the "awake" patients, 100% O_2 was administered by face mask until the seizures spontaneously ceased. Occasionally, a nasal airway was used.

In the patients to be given methohexital, morphine (up to 0.6 mg/kg), droperidol, and local anesthesia were given as described above. In addition, general anesthesia was induced with methohexital, 1 to 1.5 mg/kg, as a bolus, followed by succinylcholine for tracheal intubation. A continuous infusion of methohexital 0.1% was begun and ventilation controlled with oxygen and air to maintain a Pco_2 level of 30 mm Hg, monitored by end-tidal sampling. A non-depolarizing muscle relaxant (curare or pancuronium) was injected intermittently in doses to abolish the fourth twitch of train-of-four stimuli applied by a peripheral nerve stimulator to the ulnar nerve. The rate of methohexital infusion was determined by changes in vital signs, patient movement, and interpretation of the electroencephalogram (EEG). Typically, 10 mg/kg of methohexital was used over 6 hours. When excision of cortical tissue was completed and no further recordings were required, all intravenous agents were discontinued and N_2O added for closure. At the conclusion of the operation the muscle relaxant was reversed and extubation was accomplished with resumption of appropriate respiration and return of consciousness. Small doses of naloxone were needed in three patients.

Intraoperative Corticography

The presence and extent of the epileptogenic focus were determined by an array of 27 specially made bipolar platinum/silicone electrodes placed in three rows across the exposed surface of the brain on both sides of the Sylvian fissure and extending to the area of the central gyrus. The electrode holder was clamped to the skull. Electrodes were repositioned following excision, their positions at each stage being marked by the encephalographer on "brain diagrams" illustrating the topography of the surface of the brain. Somatosensory-evoked potentials were recorded after stimulation of face, arm, and leg, with the indifferent electrode in muscle, and the appropriate areas charted.

Surgical Technique

The patients were in a semilateral position with the head supported by a three-pin Mayfield head-holder. Following delineation of the epileptogenic focus, a localized cortical resection or temporal lobectomy was performed with bipolar cautery and suction. For smaller resections a subpial dissection was performed where possible. When the anterior temporal lobe was removed, brain tissue was removed over the Island of Reil without disturbing the underlying pia. If a small delineated area having an active electrical abnormality could not be sacrificed, subpial transverse cortical sections were performed using a small angled dissecting hook. After hemostasis was obtained, the dura was closed, the bone flap wired back in place, and the scalp closed in layers. No drains were used.

Results

Identification and Delineation of Focus

A resectable abnormal EEG focus consistent with the patient's symptoms was found at every operation.
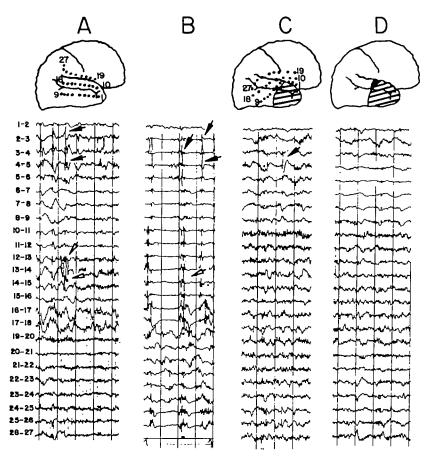
FIG 1. Intraoperative electrocorticography. Twenty seven electrodes were arrayed in three rows of nine, as shown in brain diagrams. Electrical potentials were recorded between pairs of adjacent electrodes, eight pairs for each of three rows. Closed arrows indicate epileptogenic spikes from inferior temporal gyrus. Open arrows indicate focus on adjacent superior temporal gyrus. Lower channels derive from supra-Sylvian cortex and show no abnormality. A, Before methohexital, showing epileptiform spikes against a background of normal activity. B, Before

excision, 2 minutes after methohexital, 150 mg, bolus. Spikes stand out (arrows) in relief as background activity is suppressed. Lower channels show burst-suppression pattern typical of barbiturate effect on normal brain. C, After initial excision, indicated by hatched area, and rearrangement of electrode array. Remaining abnormal spike is seen adjacent to posterior border of excision (closed arrow). D, Excision extended posteriorly, as indicated by black area. Tracing is normal.

The foci could be delineated easily in patients given methohexital because of the activation of the epileptiform activity. This is demonstrated in Fig 1 taken from the EEG record of a patient undergoing methohexital activation. The pathologic discharge in B is shown in sharp relief as background activity subsides and as secondary foci disappear. A small epileptiform discharge that persists after the initial resection (Fig 1,C) is absent following extension of the resection. In Fig 1 is shown how identification of interictal spikes and localization of the focus are enhanced. Similarly, sensory cortical-evoked responses were not suppressed and could be used to identify the postcentral gyrus. With this identification, the motor strip could be delineated. Thus, in cases where the speech center resides in the opposite hemisphere (diagnosed by

preoperative testing) these areas can be identified with the patient asleep.

Quality of Surgical Field

Controlled respiration, hyperventilation, avoidance of hypoxia, and absence of straining or moving combined to provide optimal conditions for the neurosurgeon, aided resection, and may have limited edema. In contrast, an awake patient having a seizure usually had a bulging, tense brain with visible petechiae.

Anesthetic Complications

The occurrence of generalized seizures in the awake patients created several potential hazards. Hypoxemia was frequently observed, the possibility of aspiration

caused anxiety, postictal patients were noncommunicative, and occasional acid-base disturbances were observed. One patient's seizure was temporally related to injection of the local anesthetic. An increase in temperature requiring rectal acetaminophen was seen in two patients.

These hazards were avoided in patients anesthetized with methohexital. All but two of these patients were easily extubated in the operating room. One of these two patients was a 3-year-old child who was kept intubated prophylactically. The other had a seizure on emergence and required continued intubation until this was controlled.

Many patients exhibited the need for generous amounts of intravenous drugs, possibly related to a degree of hepatic microsomal enzyme induction consequent upon long-term anticonvulsant medication. This observation applies to non-depolarizing relaxants as well as to sedatives. The same observation has been made in a similar group of patients by Messick

et al (5), but the precise mechanism has not been elucidated. Despite close monitoring of the level of paralysis, movement of the patient during surgery was not uncommon, indicating the need for additional methohexital or relaxant as appropriate. Certain maneuvers were associated with a reaction, or would elicit a complaint in the awake patients. Occasionally the dura was sensitive, particularly around the middle meningeal vessels, and produced discomfort upon opening. The dura at the base of the skull at the site of bridging venous connections with the temporal lobe was also sometimes sensitive when cauterized. One patient complained of pain when the temporal lobe around a small temporal branch of the middle cerebral artery was resected. At no other time did a patient report discomfort during the actual cortical resection.

Outcome

Improvement of Seizures. The patients were judged as "markedly improved" if they had absent or infrequent seizures on reduced medications. They were judged as "improved" if they had reduction of seizure frequency on a medical regimen. As shown in Fig 2, 88% of the patients given methohexital were improved, with 64% having marked improvement and 24% having some improvement. In "awake" patients, 91% were improved with 64% having marked improvement and 27% having some improvement. The differences in the success rates for the two groups were not significant.

Neurologic Deficits. The numbers of patients with postoperative neurologic deficits are shown in Fig 2 and described in the Table. The incidences of neurologic deficits were comparable in the two groups.

Fia 2. Outcome of surgery. Patients scored as described in text.

TABLE

Postoperative Neurologic Deficits

Patient no.	Anesthetic technique	Age	Outcome*	Deficit	Comments
		yr			
6	Methohexital (2nd operation)	20	++	Hemifacial weakness	1st operation under general anesthesia unsuccessful; deficit created to secure improvement
17	Methohexital (2nd operation)	11	++	Hemiparesis, improving	1st operation curtailed to avoid production of neurologic deficit; seizures unabated; deficit created to secure improvement
26	Awake (2nd operation)	29	++	Hemiparesis	1st operation unsuccessful; area of excision extended
28	Awake	33	++	Arm weakness, expressive dysphasia	Porencephalic cyst removed; stormy postoperative course, required V-P shunt
29	Awake	40	+	Mild dysnomia, clearing	Old arteriovenous malformation; focus extended into speech area, excision curtailed

* Key: +, improved; ++, markedly improved.

Homonymous quadrantanopsia, an almost universal finding, was not included as a deficit. Only new motor weakness or speech difficulty was considered to constitute a neurologic deficit. In two patients deficits were deliberately produced to improve the patient's epileptic status (patients 6 and 17). In patients 26 and 29, operated on awake because of the location of their foci, deficits resulted because of the proximity of the focus to the sensorimotor area. Patient 29's deficit is now almost completely resolved. Patient 28 did well initially but developed complications including subgaleal effusions, hydrocephalus, and depression. Of the five, his deficit was the only one not anticipated at surgery.

Repeated Operations

Data for three patients who underwent two procedures each are summarized in the Table. Their first operations were unsuccessful when surgery was limited because of the proximity of the focus to the motor or speech area.

Discussion

Cortical resection has gained a secure and enlarging role in the treatment of selected patients with medically refractory epilepsy. Conservatively, potential candidates comprise 10% of all patients with epilepsy. The surgical aim is to identify the total epileptogenic area so that the involved cortex can be removed as completely as possible without producing a new neurologic deficit.

Our results suggest that patients requiring resection of epileptogenic cortical foci can be given the benefits of a general anesthetic when methohexital is used without impairment of intraoperative cortical mapping. The 88% improvement following operation compares favorably both with the 67% reported by Van Buren et al. (3) in their summary of the literature and with the 91% improvement observed in our patients operated on while awake.

It is difficult to relate the incidence of neurologic deficits to anesthetic technique because patients are treated differently, depending on the severity and location of their foci. Published results (6) include only deficits produced unexpectedly and exclude patients with lesions near the sensorimotor strip. In our experience with 36 patients, only one such unexpected deficit resulted.

Although methohexital is frequently used to activate epileptic foci in diagnosis of temporal lobe psychomotor epilepsy (4, 7, 8), this is, to our knowledge, the first full description of its use both as an anesthetic and an activating agent. A similar technique is mentioned by Rasmussen (6) but only for children.

There are two reports (9, 10) of the successful use of enflurane for this dual purpose in two patients, but we believe methohexital to be superior because enflurane has been reported to elicit frank seizures as well as EEG changes in otherwise normal individuals (11). This raises the possibility that the agent might cause serious diagnostic errors or confusion.

The only contraindication to the use of methohexital general anesthesia, in our opinion, is the necessity for delineation of the speech area. Use of methohexital in the way we have outlined avoids the hazards of deliberate intraoperative awakening of the patient or the necessity for producing an awake but paralyzed and intubated patient. The disadvantages of operating for many hours on a poorly cooperative patient are circumvented without compromising accuracy. Thus, this technique offers the benefits to surgeon and patient of general anesthesia, while allowing accurate delineation of epileptic foci.

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A Double-Blind Comparison of Parenteral Morphine, Placebo, and Oral Fenoprofen in Management of Postoperative Pain

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DAVIE, I. T., SLAWSON, K. B., AND BURT, R. A. P.: A double-blind comparison of parenteral morphine, placebo, and oral fenoprofen in management of postoperative pain. Anesth Analg 1982;61:1002-5.

A double-blind study comparing parenteral morphine, 8 mg, with parenteral placebo and with oral fenoprofen, 200 mg, for the relief of postoperative pain following outpatient surgery was undertaken in 90 patients. The study drugs were administered within 2 hours of the operation and the Visual Analogue Scale was used to assess pain intensity. Patients given placebos showed minimal change in mean pain intensity, whereas patients who received morphine had significantly less pain at all assessment periods. Pain relief in patients who received fenoprofen was, for the first 2 hours, better than following placebo but not as good as following morphine, but thereafter, there was no significant difference between the morphine and fenoprofen and both were significantly better than placebo. It is concluded that oral analgesics may be a useful alternative to the traditional parenteral analgesics for outpatient surgery.

Key Words: PAIN: postoperative; ANALGESICS: fenoprofen, morphine.

TRADITIONALLY, relief of pain in the immediate postoperative period is provided by parenteral analgesics, usually one of the opioid derivatives. However, with the increasing popularity of outpatient surgery (1), it is important that patients be free of pain following the operation yet be fit enough to return home and still be able to continue receiving analgesics should these be necessary.

Fenoprofen is an arylacetic acid derivative which is thought to produce analgesia through inhibition of prostaglandin synthesis. This paper describes a double-blind study in which oral fenoprofen, 200 mg, was compared with parenteral morphine, 8 mg, and placebo using the Visual Analogue Scale (VAS) in hospital outpatients undergoing surgery. Before starting the double-blind study, a single-blind pilot assessment was undertaken and the results from this have been published (2). The present double-blind study followed an almost identical protocol and incorporated minor lessons learned from the pilot trial.

Methods

Ninety patients were enrolled in the study after the nature of the investigation had been explained to them and their consent had been obtained. All had minor surgery performed on an outpatient basis and were to be allowed to return home the same day, provided that they were accompanied. The patients had taken no drugs in the preceding 24 hours and received no preanesthetic medication. Intravenous thiopental was used for induction of anesthesia, which was maintained with nitrous oxide, oxygen, and halothane. No muscle relaxants were given and no parenteral analgesic drugs were used to supplement anesthesia. Following surgery, the patients were placed in an adjacent recovery area. When patients first complained of pain (in all cases within 2 hours of completion of surgery), they were interviewed by one of the authors and their pain intensity assessed: at the same time, the patients marked their pain intensity on a 10-cm VAS measuring from "no pain" to "pain as bad as could be."

Patients then received one of the three study drugs assigned in predetermined random order. The hos-

pital pharmacy supplied the morphine and saline injections in identical ampules and the commercially available form of fenoprofen, 200 mg, was used. Matching inert tablets were supplied by the Department of Pharmacy at the Heriot-Watt University, Edinburgh. The drugs were administered in the double-blind manner using the double-dummy technique so that each patient received an injection and a tablet. Thus, each patient received either: morphine, 8 mg, plus an inert tablet; fenoprofen, 200 mg, plus a saline injection; or a saline injection plus inert tablet.

At hourly intervals for 6 hours patients made further assessments of pain intensity using the VAS. The scales were printed on the same record form so that the patients were able to see their previous marks and the same observer was present at all assessments. "Rescue" analgesics were given on request to any patient who failed to obtain adequate pain relief. No further interview was conducted for any patient who received the rescue analgesic and patients who received the rescue analgesic did not provide further analogue scores thereafter.

For the purposes of statistical analysis, the last score recorded before administration of the rescue analgesic was repeated for each of the scheduled assessments that followed. This follows the method described by Houde and colleagues (3, 4). All observed or spontaneously reported adverse drug reactions were recorded.

Results

Patient characteristics are shown in Table 1. There were no significant differences between the treatment groups.

Each treatment group comprised 30 patients with

TABLE 1

Patient Characteristics in Each Treatment Group

	Placebo	Fenoprofen	Morphine
Sex			
Male	0	1	4
Female	30	29	26
Age (yr)			
Mean	34	36	35
Range	23–69	21–63	20–69
Body weight (kg)			
Mean	60.6	60.0	61.2
Range	45.5–85.0	39.5–83.5	45–90
Surgical procedure			
Laparoscopy	25	20	23
Dilation and curettage	4	6	3
Miscellaneous	1	4	4

initial pain intensity assessed as moderate. The patients who received placebo showed only minimal change in mean pain intensity over the 6 hours and those given morphine showed the greatest decrease in mean pain intensity (Table 2). After 1 and 2 hours, patients given morphine showed significantly greater improvement than the other two groups of patients (analysis of variance, $p < 0.05$). At the 1-hour assessment, patients given fenoprofen showed greater improvement than those who received placebo, but only at the 2-hour assessment did this reach statistical significance ($p < 0.05$). At the 3- to 6-hour assessments, there were no significant differences between the patients given morphine or fenoprofen (Figure) and the results in both groups of patients were significantly different from those observed in patients given placebos ($p < 0.05$).

Of the 90 patients 42 (47%) requested a rescue analgesic. More patients given placebo requested a rescue analgesic than did patients given morphine or fenoprofen, and this difference was statistically significant (analysis of variance, Arc sine transformation, $p < 0.05$), but the difference between patients who received morphine and fenoprofen was not significant. Twenty patients who received placebos requested additional analgesics before the 2-hour assessment was due, compared with eight patients given fenoprofen and three patients given morphine. These differences between placebo and active drug were statistically significant ($p < 0.05$). Only two patients, one given morphine and one given fenoprofen, were asleep at one of the assessment periods (6 hours in both). Adverse reactions were recorded in nine patients (Table 2).

Discussion

The reliability of the Visual Analogue Scale for measurement of postoperative pain has been described (5–7), and the results of this double-blind study showed that in our hands the method was sufficiently sensitive to demonstrate differences between placebo and morphine and fenoprofen in a comparison involving small numbers of patients.

At the 1-hour assessment, patients given fenoprofen had a mean pain intensity less than that reported by patients given placebos but greater than that reported by those given morphine. This finding may be explained by the different rates of absorption of parenteral and orally administered drugs.

Our first study (2) showed that few patients have mild pain following the type of surgery we studied, so in the present study enrollment was limited to

TABLE 2

Treatment In Patients with Moderate Pain

	Placebo	Fenoprofen	Morphine
No. of patients	30	30	30
Pain Intensity VAS*			
Initial	47.3 ± 1.66	46.6 ± 2.21	50.0 ± 2.24
1 hr	51.0 ± 3.22	38.9 ± 3.97	24.9 ± 2.90†
2 hr	46.7 ± 3.60	32.9 ± 4.83‡	18.8 ± 3.71†
3 hr	47.0 ± 3.44	28.3 ± 5.09†	16.4 ± 3.56†
4 hr	45.9 ± 3.76	26.7 ± 5.18†	16.5 ± 3.51†
5 hr	45.9 ± 3.76	25.4 ± 5.31†	15.3 ± 3.52†
6 hr	45.3 ± 3.90	24.9 ± 5.37†	14.7 ± 3.52†
No. of patients who received a rescue analgesic	24	11†	7†
Adverse reactions: no. of patients who complained (some complained of more than one reaction)	3	2	4
Complaints			
Nausea	1	—	3
Vomiting	3	2	2

* Values are means ± SEM. Abbreviation used is: VAS, Visual Analogue Scale.
† Significantly different ($p < 0.05$) from placebo.
‡ Significantly different ($p < 0.05$) from morphine and placebo.
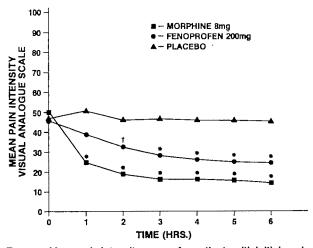
FIGURE. Mean pain intensity scores for patients with initial moderate pain. *Significantly different ($p < 0.05$) from placebo. †Significantly different ($p < 0.05$) from morphine and placebo.

patients who experienced moderate pain. Only 30% of the patients who received placebo in the double-blind study had a reduction in pain intensity of 10% or more on the VAS. This low placebo response might indicate that this clinical model provides a particularly sensitive method of assessment of relative analgesic potency.

The nature of the surgical procedures undertaken on an outpatient basis in the present study meant that most patients would be women, but the small number of men was surprising. As the male patients had met the criteria for enrollment and entered the study, it did not seem justified to exclude them a posteriori. A subsidiary analysis of variance performed on the data from female patients alone showed no change in the mean pain intensity scores in patients given fenoprofen (one man). Mean pain intensity scores in female patients who received morphine (four men) were approximately one point higher at each assessment, but this did not affect the statistical significance of the difference between the patient groups. None of the male patients given morphine requested a rescue analgesic or reported an adverse reaction. The male patient who received fenoprofen was given additional analgesia 1 hour later.

In conclusion, this study of outpatients complaining of moderate pain after minor surgery has shown that fenoprofen, 200 mg, was as effective as morphine, 8 mg, and that both active drugs were significantly more effective than placebo ($p < 0.05$). Only nine patients reported adverse reactions and these could have resulted from the general anesthesia rather than the study drugs. In a recent study, Forrest (8) has shown that zomepirac, 100 and 200 mg, another analgesic that inhibits prostaglandin synthetase, was as effective as morphine, 8 mg, in treating postsurgical pain. However, the study of Forrest differed from ours in that the drugs were not given until approximately 20 hours after surgery, whereas in our present study, drugs were given within 2 hours of surgery.

ACKNOWLEDGMENT

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Enflurane Blood-Gas Solubility: Influence of Weight and Hemoglobin

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The blood-gas partition coefficient of enflurane was measured in nine nonobese and eight morbidly obese patients and correlated with weight, body mass index, and blood hemoglobin. The enflurane blood-gas partition coefficient was lower in the obese patients than in nonobese patients (mean ± SEM: 2.03 ± 0.02 versus 1.76 ± 0.03, respectively, $p < 0.025$). There was a negative correlation between enflurane blood solubility and both body mass index and weight ($r = -0.59$ and -0.55, respectively, $p < 0.01$). A positive correlation was found between hemoglobin and the enflurane blood-gas partition coefficient ($r = 0.69$, $p < 0.01$). Equilibrium between inspired and alveolar enflurane concentration should be faster in morbidly obese and anemic patients than in healthy, nonobese patients.

Key Words: ANESTHETICS, Volatile: enflurane; BLOOD: hemoglobin; COMPLICATIONS: obesity; SOLUBILITY: blood-gas partition coefficient, enflurane.

R ECENTLY, we compared the disposition of enflurane in obese and nonobese subjects and found that arterial blood levels of enflurane rose faster in our obese patients (2). Attempting to explain this finding we preliminarily determined the enflurane blood-gas partition coefficient in a group of obese and nonobese patients and found values of 0.99 and 1.42, respectively. Although these determinations were lower than the commonly quoted value of 1.8 to 1.9 (3, 4), they are similar to the enflurane blood-gas partition coefficient of 1.3 reported by Fiserova-Bergerova and Holaday (5).

In contrast, Munson et al (6), studying 12 healthy male volunteers, observed an enflurane blood-gas partition coefficient of 1.92. The variation in blood-gas solubility coefficients for enflurane in these reports contrasts with the lack of variation in the blood-gas partition coefficient of halothane, which always has been reported as approximately 2.4 (7). The pur-

pose of this study was to redetermine the blood-gas partition coefficient of enflurane using methods that gave a blood-gas partition coefficient of halothane of approximately 2.4. Because of our previous findings, we also analyzed the influence of weight and body mass index [BMI = weight (kilograms)/height² (meters)] on the blood-gas solubility of enflurane. In addition, hemoglobin and enflurane blood-gas solubility were correlated as a positive correlation has been reported between hemoglobin and the blood-gas solubility of fluroxene, halothane, and methoxyflurane (8).

Methods

Initially, six nonobese patients were studied in the halothane group, and subsequently, nine nonobese and eight obese healthy adults undergoing elective surgery were studied as members of the enflurane group. Approval for this study was obtained from the Human Subjects Committee at the University of Arizona Health Sciences Center. All obese patients had a BMI (9) greater than 30 and a body weight at least 2 times ideal weight. All patients were A.S.A. class I or II. Patients were premedicated with diazepam (5 to 10 mg, orally) 120 minutes before and glycopyrrolate (0.2 mg IM) 90 minutes before induction of anesthesia. Each subject fasted for at least 8 hours before surgery.

For in vitro determinations of the blood-gas partition coefficient, a heparinized venous whole blood sample was obtained from each patient immediately before induction of anesthesia. A 2-ml aliquot of each blood sample was placed in a 30-ml Erlenmeyer flask equipped with a screw cap and Teflon-coated septum top. This provision allowed access to the flask's contents by syringe and needle. Liquid enflurane (3.5 to 4.0 µl) or halothane (2.0 to 2.5 µl) was then added to each flask to yield a gas phase concentration of 2.0% to 2.5% enflurane or 1.0% to 1.5% halothane. Each flask was then vented by piercing the septum with a hollow needle to equilibrate with atmospheric pressure and then shaken in a 37°C warm room for 3 hours to allow equilibration of anesthetic between gas and liquid phases. This duration of equilibration was found to be optimum and provides reproducible data. Flasks were then briefly revented to the atmosphere and shaken for another hour. Aliquots (2.5 ml) of the head space were withdrawn by gas-tight syringes and analyzed for enflurane concentration by gas chromatography utilizing a Varian 1440 gas chromatograph equipped with a SE 30 column and thermal conductivity detection. A 1-ml blood sample was simultaneously drawn and extracted with 2 ml of water-saturated n-heptane in 2-dram vials equipped with Teflon cap liners. The vials were shaken for 5 minutes and were allowed to set for 10 minutes, and an aliquot (100 µl) of the heptane layer was analyzed for anesthetic concentrations by gas chromatography. Extraction of enflurane from whole blood by this process has been shown to be in excess of 98% (10). Both gas and liquid phases anesthetic concentrations were determined in duplicate.

Gas chromatographic peak areas were compared with those of gas and n-heptane standards analyzed in identical fashion to determine enflurane concentration. Primary standards (±1% accuracy) of enflurane and halothane in nitrogen were purchased from Ohio Medical Products. Liquid heptane standards were made by adding a known volume of liquid anesthetic into a known volume of n-heptane. The blood-gas partition coefficient was calculated as anesthetic concentration (micromolar) in the liquid phase divided by the anesthetic concentration (micromolar) in the gas phase at 760 torr. All determinations are reported as means ± SEM.

Student's t-test was used for group comparisons, whereas linear correlation analyzed the influence of weight, BMI, and hemoglobin on the blood-gas partition coefficient of enflurane. Statistical significance was defined as $p < 0.05$.

Results

Initially, we found low halothane partition coefficients (2.0) using our previously described method (2). However, using the above method, which allows more extensive mixing and better equilibration of the anesthetic between the gaseous and blood phases, a halothane blood-gas partition coefficient of 2.45 ± 0.02 was found for six nonobese patients. Subsequently, we found a blood-gas partition coefficient for enflurane of 2.03 in nine nonobese patients as opposed to 1.76 in eight obese patients (Table, $p < 0.025$). The blood-gas solubility of halothane was not determined in these latter patients. The overall mean blood-gas partition coefficient of enflurane for both lean and obese patients was 1.84 ± 0.2.

Age and hemoglobin levels were similar in obese and nonobese patients given enflurane; height, weight, and BMI were, however, significantly different (Table). A negative correlation ($p < 0.01$) was found between the blood-gas partition coefficient of enflurane and both weight ($r = -0.55$) and BMI ($r = -0.59$) (Figure). In contrast, a positive correlation was found between hemoglobin and the blood-gas partition coefficient of enflurane ($r = 0.69$, $p < 0.01$) (Figure). Weight did not correlate with hemoglobin levels.

TABLE

Patient Characteristics and Enflurane Blood-Gas Partition Coefficients (B/G λ)*

Group	No. of patients	Age	Hemoglobin	Height†	Weight	Body mass Index	Enflurane B/G λ‡
		yr	g/dl	cm	kg		
Nonobese	9	42 ± 2	14.0 ± 0.2	175.9 ± 0.6	74 ± 1	23 ± 0.3	2.03 ± 0.02
Obese	8	36 ± 1	13.3 ± 0.2	163.4 ± 0.5	108 ± 1	41 ± 0.5	1.76 ± 0.03

* Values are means ± SEM.
† $p < 0.001$.
‡ $p < 0.025$.
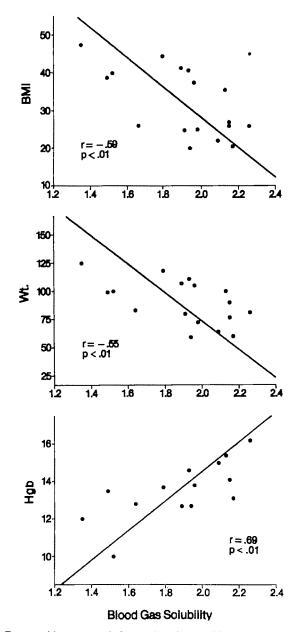
FIGURE. Linear correlations of enflurane blood-gas partition coefficient with body mass index (BMI), weight (kilograms), and hemoglobin (grams per deciliter).

Discussion

The blood-gas partition coefficient of enflurane in the obese patients was 1.76, whereas in the nonobese patients a value of 2.03 was obtained. As the methods used to determine these values also yielded a value for halothane in agreement with the vast number of determinations already reported in the literature, the values obtained for enflurane are probably accurate. Thus, our findings confirm those of Munson et al (6),

who reported a mean enflurane blood-gas solubility of 1.92.

The lower enflurane blood-gas partition coefficient previously reported by our group (2) was likely in error as subsequent investigation demonstrated that low halothane blood gas partition values were obtained utilizing the same methods. As a result, our method of determining blood-gas parirition coefficients was changed. Anesthetic equilibrium between gas and blood was extended to 3 hours. Also gas standards were purchased rather than prepared in our laboratory. With these changes, commonly accepted values for the blood-gas partition coefficient of halothane were obtained.

The blood-gas partition coefficient of enflurane was significantly lower in obese patients than in lean patients. This finding confirms our previous report (2), but is surprising as the blood-gas solubility of halothane appears to be positively correlated with increasing weight (11). The latter probably occurs because the blood solubility of halothane is positively correlated with blood levels of triglycerides (12), cholesterol (13), and total lipids (13), each of which may be elevated in obesity (14). Similar studies with enflurane have not been performed. Nevertheless, logically similar positive correlations between these blood components and enflurane blood solubility should increase rather than decrease the enflurane blood-gas partition coefficient of enflurane in morbidly obese patients.

Thus, obese patients must have change in blood components other than triglycerides, cholesterol, and total lipids to account for our findings. Increasing weight is associated with decreased concentration of high density lipoprotein. Although undocumented, quantitative alterations in other serum protein fractions may occur in obese patients, which could lower the blood-gas solubility of enflurane in these patients. Clearly, further investigation analyzing the relationship between various blood components, weight, and the enflurane blood-gas partition coefficient are required.

In contrast to weight, increasing concentrations of hemoglobin were associated in this study with increasing enflurane blood-gas solubility. This has also been shown to be true for fluroxene, halothane, and methoxyflurane (8). This finding is important as large changes in enflurane solubility (range 1.52 to 2.26) were found as hemoglobin levels varied between 10.0 and 16.2. These hemoglobin values are encountered clinically and could be expected to influence anes-

thetic uptake in concert with alterations in enflurane blood-gas solubility.

In summary, this study showed that the blood-gas partition coefficient of enflurane is lower in obese than in nonobese patients, correlates positively with hemoglobin, and is in overall agreement with the traditionally stated values of 1.8 to 1.9 despite reports in the literature to the contrary. Equilibrium between inspired and alveolar enflurane concentrations should be achieved more rapidly in both morbidly obese and anemic patients than in nonobese patients with normal hemoglobin concentrations.

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technical

COMMUNICATION

Digital and Sampled-Data Control of Arterial Blood Pressure during Halothane Anesthesia

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A control system that maintains mean arterial pressure (MAP) at a desired level by automatically controlling halothane input has been developed. The control system is a discrete, digital type and is implemented with a small desk-top programmable calculator. Essentially, if MAP decreases, the inspired concentration of halothane will decrease; if MAP increases, the system will compensate by increasing inspired halothane concentration. The control system was tested in two ways: with a hybrid computer model of uptake and distribution of halothane and with dog experiments. The results indicate that (a) the model can be used to predict the response of the animal-anesthesia machine control system, and (b) the proposed algorithm is successful in controlling one anesthetic agent with one physiologic variable.

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Automatic control systems will probably help improve the safety of anesthesia, as well as help anesthesiologists with boring tasks. Several workers have successfully controlled the administration of a single agent with a single physiologic variable: thiopental or cyclopropane with electroencephalograms (EEG) (1-4); halothane with heart rate (5); halothane (6, 7), norepinephrine (8), or nitroprusside (9) (Slate JB. Model-based design of a controller for infusing sodium nitroprusside during post surgical hypertension. PhD thesis. University of Wisconsin, Madison, WI, 1980.) with arterial pressure; muscle relaxants with muscle twitch (7); and ventilation with CO_2 (7, 10). These systems have generally used analog controllers based on proportional-, integral-, and derivative-control laws.

This report describes the use of a discrete digital-control (DDC) system. The delivered concentration of halothane was controlled automatically to maintain mean arterial blood pressure (MAP) at a desired level by using a discrete time-optimal control algorithm. We also demonstrated the feasibility of using a hybrid-computer model of the uptake and distribution of halothane in the testing of the control algorithm, thus minimizing preliminary animal experiments.

Methods

Two sets of experiments were conducted. First, we performed a computer simulation of the proposed animal experiments, in which a hybrid-computer multiple model of the uptake and distribution of halothane (11, 12) substituted for a dog and an anesthesia machine. In the other set, the MAP of each of six dogs was kept at a desired level by automatically controlling the delivered concentration of halothane.

Control Algorithm

Essentially, the DDC averages blood pressure for a set interval (T), which is 20 seconds in the present system. It reviews the five previous consecutive intervals, takes into account the MAP and inspired halothane concentration (H_i) for each interval, and decides on the inspired concentration for the next interval. One can set the desired pressure (set point pressure)

to any reasonable level, and the system will administer the appropriate amount of halothane to maintain that set point under the given circumstances. Thus, if a disturbance such as surgical incision or hemorrhage occurs, the system should change inspired halothane concentration appropriately. The following describes the control algorithm used to effect the above. The same control algorithm was used for both sets of experiments. Discrete sampled values of past input (halothane) and output (MAP) variables are used as the input to the control system.

A sampled value, $R(-nT)$, at n previous sampling times is described by

$$R(-nT) = \int_{-(n+1)T}^{-nT} MAP \, dt$$

where MAP = mean arterial pressure and T = 20 seconds.

The averaged pressure, $MAP(-nT)$, between $-(n + 1)T$ and $-nT$ may be given by

$$MAP(-nT) = \frac{R(-nT)}{T}$$

from which the error, $E(-nT)$, between the averaged pressure, $MAP(-nT)$, and the desired pressure, $\overline{DP}(-nT)$, at n previous sampling times is described by

$$E(-nT) = MAP(-nT) - \overline{DP}(-nT)$$

The integral of the error, $I(-nT)$, at n previous sampling times is

$$I(-nT) = T\{MAP(-nT) - \overline{DP}(-nT)\} + I\{-(n+1)T\}$$

The control formula to determine the delivered halothane concentration is expressed by

$$H(0) = \sum_{i=1}^{5} \{a_iH(-iT) + b_i[E(-iT) + K_I(-iT)]\}$$

where $H(-nT)$ (for n = 0, 1, ...5) = the delivered halothane concentrations, and a_i, b_i, and K_I are constants.

This formula states that the five most recent halothane concentrations, pressure errors, and values of integrated pressure error are used to determine the next delivered halothane concentration. The device adjusts the delivered halothane concentration to bring the pressure to the desired level as rapidly as possible.

We estimated the coefficients a_i and b_i (i = 1, 2, ... 5) on a digital computer. Based on the experimental data obtained by Smith and Schwede (6), the discrete transfer function between inspired halothane concentration and mean arterial pressure was esti-

mated by the Steiglitz algorithm (13), a discrete time-optimal control algorithm, with n = 5 and T = 20 seconds.

Computer Simulation

Before we performed closed-loop control experiments in dogs, we simulated the experiments on a computer to test the performance of the proposed control system. A hybrid computer multiple model for the uptake and distribution of halothane (11, 12) was used to substitute for the dog and the anesthesia machine, with the control system inserted. To test the stability and rapidity of the system response, we introduced several types of step changes into the model: (a) arterial pressure set point, (b) systemic vascular resistance, and (c) myocardial contractility. The first step was designed to determine how rapidly the system could respond to the anesthetist's command, the second two steps to determine the response to simulated causes of rapid changes in blood pressure such as might be anticipated with surgical incision, sudden hemorrhage, or inadvertent administration of a vasodilator.

Experiments in Dogs

Encouraged by the model's success, and armed with coefficients that we knew were "close," we performed closed-loop experiments with mongrel dogs. Anesthesia was induced and maintained with halothane-oxygen only in six dogs weighing 21.2 to 26.5 kg. Rectal temperature and end-tidal CO_2 were measured and maintained at normal levels (37.5 to 39.0°C and 32 to 34 torr, respectively), the former with a heat lamp, and the latter with controlled ventilation via an endotracheal tube.

A schematic diagram of the basic closed-loop experimental setup is given in Fig 1. The delivered
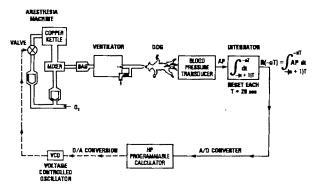
Fig 1. Schematic diagram of closed-loop control system for dog experiments.

concentration of halothane was precisely regulated by an electronically controlled needle valve, which determined the flow rate of O_2 through a constant-temperature vaporizer (Ohio Medical Products DM-5000) and thus determined the delivered halothane concentration. The control signal regulated the needle position of the valve via an electrically controlled box. Gases from the anesthesia machine passed into a 0.5-L rubber bag and then into a Harvard (non-rebreathing) ventilator. All connecting tubings were kept as short as possible to minimize gas transit times. Arterial pressure was measured via a catheter inserted percutaneously into the femoral artery and connected to a Statham P 37 continuous-flush transducer. The signal was meaned in two ways—continuously with electronic meaning, and every interval (T) so that a voltage equivalent to the MAP was produced every 20 seconds. The latter was accomplished by integrating and resetting the blood pressure signal every 20 seconds, thereby giving a voltage proportional to MAP. The output of the integrator was sampled and passed into a Hewlett-Packard 9810A programmable calculator via a homemade analog-to-digital converter. The calculator was then used as the digital controller. The control signal (via digital-to-analog conversion from the calculator) was fed into the control box, which in turn regulated the valve opening and closing, and thus regulated the delivered halothane concentration.

We introduced several types of disturbances to test the control system performance: (a) a step change in the arterial pressure set point, (b) an infusion of phenylephrine (46 to 92 µg/min), (c) an infusion of nitroglycerin (184 to 368 µg/min), and (d) the introduction of two to three breaths of amyl nitrite into the ventilator. The last three were done only to acquire a preliminary estimation of the performance and stability of the system.

The first disturbance was used in a more formal trial. For it, we told the machine to change set point from 80 to 50 torr and, after a suitable steady state, back to 80 torr. For each step change, there were four performance criteria: (a) rapidity of change (time to 90% of final value), (b) magnitude of overshoot, (c) time to attain within 2 torr or better of the set point for 1 continuous minute (settling time), and (d) the closeness with which the set point was maintained for 5 continuous minutes (stability).

All information was recorded on a Hewlett-Packard strip-chart recorder. The information included continuous (filtered) MAP, magnified continuous MAP, magnified discrete MAP, and inspired halothane con-

centration. The 90% rise time, overshoot, time to ±2 torr for 1 minute, and the integrated error for 5 minutes were extracted from the strip chart. The integrated error was calculated as the sum of the absolute errors from the set point as measured every 20 seconds. We could read to the nearest 0.2 torr.

Results

The tests run with the hybrid model revealed that the control algorithm performed well in the "average" dog, although they did suggest that relatively small changes in the condition of the animal, such as variations in blood volume, would produce instability in the control system. The ability to adjust to changes in state is important in a device that is to control anesthesia in a large variety of patients under a large variety of circumstances without the need for time-consuming adjustments by the anesthesiologist. The computer simulation for step changes in mean arterial blood pressure set point (70 to 50 torr and back to 70 torr) is shown in Fig 2.

Arterial pressure reached the desired level in approximately 5 minutes, then overshot and returned gradually to the desired level. A preliminary experiment in which the arterial blood pressure set point was changed from 75 to 50 mm Hg and back to 75 mm Hg is shown in Fig 3. This test is comparable to the test performed in the model (Fig 2), as are the results. The pressure decreased to 50 mm Hg in approximately 8 minutes, with no overshoot, and increased to 75 mm Hg in approximately 10 minutes. The coefficients used were the same for both the dog
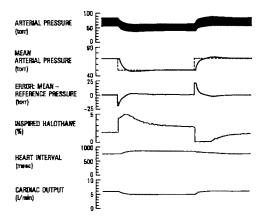
Fig 2. Results of hybrid computer simulation of step changes in arterial-pressure set point. Initially, simulated pressure is at set point of 70 mm Hg. When set point is changed to 50 mm Hg, control system automatically adjusts halothane input to reduce pressure to that level. As desired arterial pressure is changed back to 70 mm Hg, control system reacts accordingly.

and the hybrid model, with only the gain constants changed to take into account the individual animal of the experiment, as opposed to the average dog of the model. The performance of the controller during the step tests is summarized in the Table.

The reaction of the dog and control system to a 46 μg/min continuous infusion of phenylephrine is shown in Fig 4. The control system compensates for
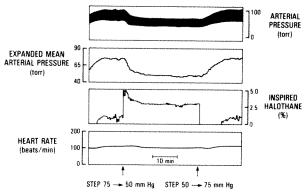
FIG 3. Results of canine experiment in which arterial pressure set point was changed from 75 to 50 mm Hg and back to 75 mm Hg. This test and results are comparable to computer simulation in Fig 2. Control system coefficients are the same in both cases, except for one gain constant (K').

TABLE

Response of Controller to Steps from 80 to 50 or 50 to 80 Torr Mean Arterial Pressure (MAP)*

	Decreasing MAP	Increasing MAP
Time to 90% (sec)	211.5 ± 41.5	199.0 ± 25.7
Overshoot (%)	−14.5 ± 11.3	17.4 ± 10.2
Settling time (sec) (±2 torr for 1 min)	435.0 ± 257.9	474.7 ± 170.3
Stability for 5 min (torr sec)	416.4 ± 117.1	425.3 ± 266.5

* Values are means ± SD.
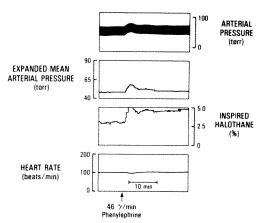
FIG 4. Effect of 46 μg/min continuous infusion of phenylephrine. Increase in arterial pressure is compensated for by control system, which increases level of halothane input.
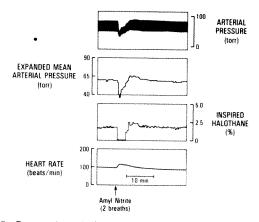
FIG 5. Dog and control system reaction to sudden transient decrease in arterial pressure caused by introduction of two breaths of amyl nitrite into the ventilator. Control system reacts to sudden decrease by turning off halothane, thereby bringing pressure back to desired level much faster than if anesthetic level had remained constant.
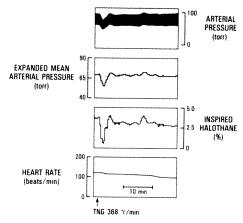
FIG 6. Response to continuous infusion of 368 μg/min of nitroglycerin (TNG). Control system reacts to sustained decrease in arterial pressure by reducing halothane input sufficiently to compensate for it.

the increase in MAP by increasing the delivered halothane concentration. At no time, after preliminary setup, did we enter a value for halothane. The control algorithm predicts the needed level by the animal's reaction to previous values. The effect of a sudden transient decrease in pressure induced by two breaths of amyl nitrite introduced into the ventilator is shown in Fig 5. This represents a bolus injection of a drug, in contrast to the continuous infusion demonstrated in Fig 4. The control system reacts almost immediately to the pressure decrease by discontinuing halothane, and then resumes administration of halothane when the arterial pressure increases sufficiently.

The response to a rapid decrease in arterial pressure during a continuous infusion of nitroglycerin at a rate of 368 μg/min is shown in Fig 6. The compensation

by the control system is again rapid and is maintained until the infusion is discontinued.

Discussion

Automatic control of delivered halothane concentration has been developed to maintain arterial blood pressure at a desired level. Our results indicate several important points: (a) Digital and sampled-data control techniques can be used to develop a useful digital controller. (b) A computer model of anesthetic uptake and distribution can be used to test the control algorithm and thereby reduce the number of preliminary animal experiments. The main function of the hybrid computer model was to determine whether the coefficients obtained from the digital computer would effect useful control. Having determined that this was so, we fine-tuned the coefficients to achieve optimal control. (c) The present automatic control was performed with a desk-top calculator having significant constraints as to memory and computation capabilities. This indicates that a special-purpose microprocessor system can be developed, thereby significantly decreasing the cost of this control system. Such an inexpensive and small control system can easily be made part of the anesthesia machine.

Why did we not use conventional control theory to effect our control algorithm? There are several advantages of the DDC over a conventional analog approach. These include the easier implementation of multivariable control, sequential control (for start-up, shutdown, or emergency operation), adaptive control, and overall supervisory control. We recognize, for example, that a single variable could not be used to control halothane concentration, as there are multiple causes for changes in arterial pressure which might require an action other than altering halothane concentration. An advanced anesthesia control system, our ultimate goal, would use many variables, such as blood pressure, end-tidal anesthetic, and CO_2 concentrations to control the anesthetic agents, drugs, and fluids, as well as ventilation, in order to keep physiologic variables such as cardiovascular, respiratory, central nervous system, and neuromuscular variables at desired levels. Direct-digital control may be a powerful approach to establish such an advanced system.

Our DDC is unique in at least one respect. It is the only system to use both the control and the controlled variable to effect control. In other words, it not only uses MAP it also uses halothane concentration in deciding what concentration to use over the next time period. This allows us to follow the concentration of halothane producing the current and past values of

blood pressure and thus to select the next concentration more accurately. In addition, the use of the last five intervals in the control algorithm is a rather nontraditional approach. In essence, this approach substitutes for the integral term in the conventional proportional-integral-derivative type of control system. In the latter, the integral contains information of past events.

There are many reasons for using arterial pressure as a control variable. It is relatively easy to measure. Methodology for measuring MAP has vastly improved over the past decade, particularly with regard to accuracy and reliability. In uncomplicated cases, it reflects the depth of anesthesia with halothane (6, 14). Many anesthetists use blood pressure to help decide the inspired concentration of halothane. For example, if blood pressure decreases, the anesthetist often decreases the inspired concentration of halothane. The present system can help keep MAP within a narrow, desired range.

This system is potentially useful in several situations. Hypertension can cause problems in patients with coronary artery disease, and halothane is often used to help decrease blood pressure. Furthermore, with most agents, the anesthetist will increase the depth of anesthesia if it is felt that light anesthesia is causing hypertension. If blood pressure were to increase sharply, as for example following tracheal intubation or surgical incision, with the present system halothane would be adjusted rapidly to compensate for the increase in pressure, yet would taper off when the stimulus disappeared or diminished. Similarly, if a particularly stimulating portion of surgery was taking place, the concentration of halothane would increase appropriately. During the less stimulating portions of the operation, the concentration would be lower, again appropriately. Conversely, if arterial pressure were to decrease suddenly, as during brisk hemorrhage or vagal stimulation, the system would respond in the most appropriate fashion—by shutting off the halothane. It should be pointed out that the system responds not only to a change in pressure, but also to how rapidly the pressure changes. Thus, a sudden decrease in pressure is more cause for alarm and vigorous response than is a gradual change.

The control system performed within clinical expectations, although comparison with other anesthetic control systems is difficult as our methods of testing have not been used before with clinical control systems, and our control variables have rarely been used. Particularly significant, however, is the fact that once the gains are properly set, the system does not oscil-

late, even with a sudden decrease or increase in pressure. Yet it still manages to effect a rapid response to rapid changes in pressure. In other words, it responds optimally to changes in pressure. A quickly responding control system is important, because rapid changes can occur in MAP, and equally rapid adjustment is essential. The present system is continually observing the blood pressure and can usually respond more quickly than can most anesthetists.

At least three problems exist with the present system. Currently, the system is only usable in patients in whom direct, continuous arterial pressure is being measured. However, new devices for noninvasive, beat-to-beat measurement of blood pressure will soon be available (15). These will increase the number of patients in whom the system will be useful. Accurate MAP measurement is, of course, mandatory. However, let us consider the consequences of an inaccurate pressure. If pressure reads artifactually too low, halothane will be shut down or off. This is an alarm condition, and the anesthetist will be alerted. The cause is usually a small clot in the cannula. This can be, and should be, prevented by a continuous flush system. Rarely does MAP read too high artifactually. The circumstances under which that could occur would include poor calibration technique, a drifting amplifier, or raising the operating table in relation to the transducer. The first can be prevented by reasonably careful technique, the latter by attaching the transducer to the table. If significant hypertension or hypotension occurs, or if the MAP is changing rapidly, the system can alarm to alert the anesthetist, who may be concentrating on other aspects of the anesthetic management.

Several system gains must be set to achieve an optimal response. These gains vary from animal to animal and as conditions change. For example, a change in ventilation is tantamount to changing the internal gains of the animal, and the system gains must be reset. For a final, clinically useful system, an adaptive system is necessary, that is, one that can adapt to a given animal and then change its gain in response to changing conditions. The DDC described should help achieve an adaptive system.

In summary, we have described a discrete-digital feed back control system for controlling the concentration of halothane with mean arterial blood pressure. The use of DDC represents a significant improvement over previous control systems. However, several improvements must be incorporated before the system is ready for routine use in patient care. These include alarms, fail-safe devices, adaptive control, and multivariable control. This paper has described a first step toward this system and to the multivariable system described above.

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CLINICAL reports

Hydralazine for Controlled Hypotension during Neurosurgical Operations

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Robert F. Bedford, MD†

Controlled hypotension is often used during neurosurgical procedures to reduce operative blood loss or to prevent rupture of cerebral aneurysms. Sodium nitroprusside is probably the most frequently used hypotensive agent despite several undesirable characteristics which include: cyanide toxicity (1), tachyphylaxis (2), highly variable dose response (3), rebound hypertension (4), changes in venous admixture (5), and technical difficulties created by the need for light-protected solutions and precision infusion systems. Because of these problems we initiated a search for an alternative technique. This report summarizes our experience using intravenous hydralazine during low-dose enflurane anesthesia for providing controlled hypotension during neurovascular procedures in a group of eight patients.

As vasodilators such as hydralazine have been found to increase intracranial pressure (ICP) in patients with severe brain injuries (6), we also examined the effects of hydralazine on ICP when used for control of intraoperative arterial hypertension in a second group of eight patients undergoing craniotomy for excision of supratentorial tumors.

Methods

Part 1

Seven patients (28 to 63 years of age) undergoing elective craniotomy for clipping of cerebral aneurysms and one patient (27 years of age) undergoing excision of an arteriovenous malformation were studied both before, during, and after controlled intraoperative hypotension. The study was approved by the local human studies committee. Seven patients were A.S.A. physical status II or III; one patient was A.S.A. class IV. With the exception of two patients who had preexisting hypertension, all subjects were free of significant cardiopulmonary disease, and classification of patients in A.S.A. classes III and IV was related only to the recent onset of neurologic symptoms.

Radial arterial and thermistor-tipped pulmonary arterial catheters were placed percutaneously under pressure waveform control and electrocardiogram lead II was monitored. Heart rate, radial arterial, pulmonary arterial, and central venous pressures were continuously transduced (Bentley model 800 transducers) and recorded (Brush model 440 recorder). Cardiac output was determined in triplicate by the thermodilution technique (Edwards model 9520A computer) using a 10-ml bolus injection of room temperature 5% dextrose in water. Body surface area was determined from standard nomograms for height and weight. Arterial and mixed venous blood samples were drawn anaerobically and analyzed for pH, gas tensions, and oxygen content using a Corning model 175 automatic blood gas and pH system corrected for patient's temperature and hemoglobin values. Derived cardiovascular variables and venous admixture were calculated using standard formulas.

Four patients were alert before surgery and received morphine sulfate, 0.1 mg/kg IM, and glycopyrrolate, 0.2 mg IM, as premedication. The remaining four patients were somnolent before surgery and were brought to the operating room without premedication. Anesthesia was induced with sodium thiopental, 3 to

5 mg/kg IV, and lidocaine, 1.5 mg/kg IV, and tracheal intubation was facilitated with a combination of intravenous pancuronium (0.05 mg/kg) and d-tubocurarine (0.15 mg/kg). Anesthesia was maintained with nitrous oxide (60 to 70% in oxygen), morphine (0.3 mg/kg IV), and low inspired concentrations of enflurane (0.7% ± 0.2% [SE]). Ventilation was controlled to maintain arterial P_{CO_2} between 27 and 32 torr. All operations were performed with patients in the supine position.

Hypotension was induced and maintained with intravenous injections of hydralazine, 5 to 10 mg, given every 5 minutes until the desired level of hypotension was achieved. The inspired concentration of enflurane was also increased to 1.1% ± 0.3% (SE) during the hypotensive period. Target mean arterial pressures during induced hypotension were 55 to 65 torr in patients without a previous history of hypertension and 75 torr in the two patients with a history of hypertension. Intravascular volume was maintained near preoperative values by infusion of crystalloid solutions or whole blood sufficient to maintain constant right atrial and pulmonary capillary wedge pressures. Once the surgeon achieved control of the aneurysm or vascular malformation, no further hydralazine was given, enflurane was discontinued, and anesthesia was maintained only with nitrous oxide in oxygen while blood pressure was allowed to return to prehypotensive levels. Blood pressure was monitored for evidence of rebound hypertension during the remainder of the operation and for 1 hour after surgery in the surgical intensive care unit.

Hemodynamic responses were measured and arterial and mixed venous blood samples were drawn (a) during surgical dissection before induction of hypotension, (b) after controlled hypotension was established, (c) after blood pressure was allowed to return toward prehypotensive levels.

Data obtained during and after controlled hypotension were compared with prehypotension values by analysis of variance and least significant difference testing. $p < 0.05$ was regarded as statistically significant.

Part 2

The effect of intravenous hydralazine on ICP in patients with compromised intracranial compliance was studied in eight additional patients undergoing excision of supratentorial tumors. A subarachnoid bolt and radial arterial cannula were placed before surgery under local anesthesia and pressures were continuously transduced and recorded. Anesthesia

was induced as described above and maintained with N_2O (70% in oxygen) and morphine, 0.3 mg/kg IV. Tracheal intubation was facilitated with pancuronium, 0.1 mg/kg IV, and ventilation was controlled (Pa_{CO_2} 28 to 34 torr). When arterial hypertension occurred during scalp dissection, each patient received a single dose of hydralazine , 10 to 30 mg IV, depending on the magnitude of hypertension observed. Peak changes in mean arterial pressure and ICP were tabulated from the calibrated strip-chart records in the period from 5 to 10 minutes after hydralazine was given. Statistical comparisons were performed using Student's t-test for paired data. $p < 0.05$ was regarded as statistically significant.

Results

Part 1

During neurovascular operations the combination of hydralazine and enflurane produced adequate reductions in arterial pressure and satisfactory surgical conditions in all eight patients. Six patients required only one dose of hydralazine to reach target levels of blood pressure. In these patients, mean time from injection of hydralazine to stable hypotension was 5.8 ± 2.0 (SD) minutes. The two remaining patients required, respectively, two and three doses of hydralazine before hypotension was achieved, with a delay of 14 and 21 minutes between the first hydralazine injection and the time stable hypotension was achieved. The duration of hypotension varied from 5 to 87 minutes, depending on surgical requirements. The mean time to achieve prehypotensive blood pressure after enflurane and hydralazine were discontinued was 20.8 ± 5.7 (SD) minutes. The total dose of hydralazine administered ranged from 5 to 45 mg (mean = 17 mg).

The hemodynamic findings during cerebrovascular operations are summarized in the Table. Controlled hypotension was characterized by a significant reduction in systemic vascular resistance, whereas cardiac index, stroke volume, heart rate, and cardiac preload remained stable. Values for Pa_{O_2}, pH, and calculated venous admixture were unchanged during controlled hypotension. After termination of controlled hypotension, there was no further requirement for vasoactive agents, and no evidence of rebound hypertension was found in any patient. Mean arterial pressure during the first postoperative hour was 97 ± 10 (SD) torr.

Part 2

The observed changes in ICP and mean arterial

TABLE

Hemodynamic Changes during Hydralazine-induced Hypotension*

	Before hypotension	During hypotension	After hypotension
MAP	93 ± 3.3	63 ± 2.4†	85 ± 3.8
RAP	5.8 ± 0.9	6.8 ± 1.1	7.0 ± 1.1
PAP	14.4 ± 1.2	15.6 ± 1.0	15.2 ± 0.9
PCWP	7.5 ± 0.6	7.9 ± 0.8	8.3 ± 0.7
CI	2.4 ± 0.2	2.8 ± 0.3	3.0 ± 0.4
SVR	1722 ± 135	1007 ± 114†	1344 ± 217
HR	79 ± 6.6	86 ± 5.9	83 ± 6.3
SVI	31 ± 2.4	32 ± 2.8	37 ± 3.9
SWI	35.9 ± 2.9	23.7 ± 2.2†	38 ± 4.9
QA/QT	14 ± 4.0	13 ± 2	17 ± 3.0
pH	7.55 ± 0.02	7.55 ± 0.01	7.55 ± 0.01

* Values are means ± SE. Abbreviations used are: MAP, mean arterial pressure (torr); RAP, right atrial pressure (torr); PAP, mean pulmonary artery pressure (torr); PCWP, pulmonary capillary wedge pressure (torr); CI, cardiac index (L/min/m²); SVR, systemic vascular resistance (dyne·sec·cm⁻⁶); HR, heart rate (beats/min); SVI, stroke volume index (ml/m²); SWI, stroke work index (g·m/m²); QA/QT, venous admixture (% cardiac output).

† $p < 0.05$ versus prehypotension value.

pressure in the eight patients with brain tumors are shown in the Figure. Within 10 minutes of giving hydralazine, ICP increased in four patients, decreased in one patient, and remained essentially unchanged in the remaining three patients. No patient required any measures to reduce ICP after hydralazine was given and the mean change in ICP values was not statistically significant.

Discussion

These data indicate that intravenous hydralazine affords a simple, smooth, and effective technique for achieving controlled hypotension during enflurane anesthesia. Enflurane is an integral part of this technique for several reasons: (a) it probably potentiates the hypotensive effect of hydralazine in a manner similar to its potentiating effect on nitroprusside (7), (b) increased inspired concentrations of enflurane at the beginning of controlled hypotension probably shorten the time to onset of hypotension; and (c) if blood pressure had decreased to less than target levels after hydralazine, enflurane could have been discontinued and excessive hypotension avoided. However, it was never necessary to decrease the inspired enflurane concentration once hypotension was initiated, and stable hypotension could be maintained easily with repeated hydralazine doses. The primary clinical advantage of this technique is the smooth, gradual

cardiovascular response, without "mountain and valley" blood pressure records, without evidence of arterial hypoxemia, and without rebound hypertension. Thus, although nitroprusside is currently the agent most frequently used for inducing controlled hypotension, we found that use of hydralazine and enflurane avoided many of the problems that we and others (1-5) have encountered during the use of nitroprusside.

The hemodynamic measurements during controlled hypotension in the present study reflect the combined effects of both hydralazine and enflurane on the cardiovascular system. The primary cause of arterial hypotension was a marked reduction in systemic vascular resistance. The resultant reduction in afterload, in turn, probably minimized the negative inotropic effects of enflurane anesthesia (8). Thus, cardiac index and stroke-volume remained remarkably constant during controlled hypotension, whereas
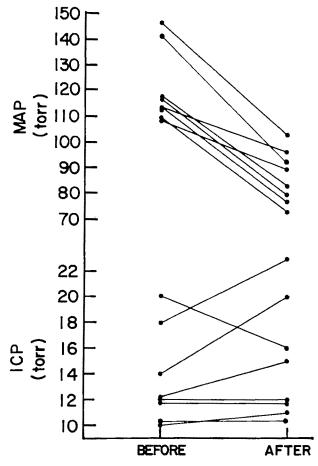
FIGURE. Effect of hydralazine on ICP and mean arterial pressure in hypertensive patients with brain tumors.

stroke work index decreased with the reduction in arterial pressure.

Hydralazine should be used with caution in patients with compromised intracranial compliance. Although we found relatively small changes in ICP after hydralazine in hyperventilated patients with brain tumors, much larger increases in ICP have been found when patients with diffuse cerebral injury and impaired autoregulation were given hydralazine to control neurogenic hypertension (6). Like nitroprusside (9) and nitroglycerin (10), hydralazine should be withheld from patients with intracranial pathology until either the dura is opened or until an ICP monitor has been inserted so that appropriate measures can be taken to control ICP, if necessary.

In summary, we have found that hydralazine, given during enflurane anesthesia, is a simple, smooth, predictable, nontoxic technique for producing controlled hypotension during neurovascular operations. We believe it is an attractive alternative to other currently available hypotensive techniques and is worthy of further evaluation.

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Convulsions: An Unusual Response to Intravenous Fentanyl Administration

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Intravenous fentanyl in doses of 100 to 150 $\mu g/kg$ are today being used in cardiac anesthesia (1). The popularity of this technique has been due in part to stability of the cardiovascular system during induction of anesthesia and to suppression of stress responses to surgery (2, 3). The few complications associated with fentanyl-oxygen anesthesia include chest rigidity during induction of anesthesia (4, 5) and awareness and recall of the intraoperative events (6) in the postoperative period. Recently we encountered five cases of generalized seizures during the rapid intravenous administration of fentanyl and we report two of these cases.

Case Reports

Case 1

A 56-year-old man, weighing 57 kg, was scheduled for elective double aortocoronary reverse saphenous vein grafting. Past history was unremarkable except for angina. He had no history of transient cerebral ischemic attacks or generalized or localized seizure disorders. He was taking propranolol, 40 mg, every 6 hours for angina. Laboratory data were within normal limits. One hour before surgery, the patient was premedicated with 8 mg of morphine sulfate intramuscularly and 10 mg of diazepam orally. Under local anesthesia, two peripheral veins, a radial artery, and the right internal jugular vein were cannulated. A triple-lumen, thermistor-tipped pulmonary arterial catheter was positioned before induction of anesthesia. Arterial blood gas tensions during spontaneous breathing of room air in supine position were within normal limits. A well fitting face mask was applied to the face and 100% oxygen was administered through a semiclosed circle system with 5 L/min oxygen

flow. An infusion of 120 ml of fentanyl (50 $\mu g/ml$) was begun. Following 20 ml of fentanyl in 30 seconds and assisted ventilation with 100% oxygen throughout, to achieve rapid unconciousness, it was decided to give a 30-ml bolus injection of fentanyl (50 $\mu g/ml$) into the intravenous infusion close to the patient. Within 45 seconds the patient developed generalized convulsions similar to grand mal seizures and arterial blood pressure increased to 170/90 torr. Succinylcholine (100 mg) was administered intravenously to facilitate ventilation and tracheal intubation. A heparinized arterial blood sample drawn immediately following intubation had a pH of 7.43, P_{CO_2} 43 torr, P_{O_2} 424 torr, and normal electrolyte values. Anesthetic and postoperative course was uneventful and an electroencephalogram performed in the immediate postoperative period was normal.

Case 2

A 47-year-old white man, weighing 80 kg, was scheduled for triple coronary artery bypass grafting. The patient had no significant medical history except for angina, which was controlled with propranolol, 60 mg, every 6 hours. Laboratory data were within normal limits. The patient was premedicated with morphine sulfate, 10 mg IM. and diazepam, 10 mg, orally 1 hour before the anticipated time of surgery. Following placement of monitoring equipment as in the first case, lorazepam, 2 mg, was administered intravenously. Anesthesia was induced with infusion of 2500 μg of fentanyl. To achieve rapid unconsciousness, another 1500 μg of fentanyl was rapidly injected into the intravenous infusion over a period of 20 seconds. Within 20 seconds following completion of bolus fentanyl injection, the patient developed generalized convulsions. By this time, the patient had received a total of 45 ml of fentanyl (50 $\mu g/ml$). Immediately 150 mg of thiopental and 100 mg of succinylcholine were administered intravenously to facilitate ventilation and intubation and to antagonize the convulsions. Hemodynamic parameters remained stable and arterial blood gas tensions immediately after endotracheal intubation were normal. Intraoperative and postoperative course was uneventful and an electroencephalogram performed in the immediate postoperative period was normal. During the convulsions, which occurred immediately following bolus injection of fentanyl, an arterial blood sample had a plasma level of fentanyl of 620 ng/ml.

In the other three cases the events were similar, with convulsions occurring immediately following a bolus injection of 20 to 30 ml (50 $\mu g/ml$) of fentanyl. There was no history of convulsive disorders in any of these patients and findings from the postoperative electroencephalograms were normal.

Discussion

Although high-dose fentanyl-oxygen anesthesia

has only recently been introduced in cardiac anesthesia, it has become popular because of hemodynamic stability during induction of anesthesia as well as during laryngoscopy and intubation (1). However, with accumulation of experience, various undesirable side effects have been attributed to fentanyl-oxygen anesthesia, including rigidity during induction of anesthesia (5), hypertension secondary to surgical stimulus (2), and awareness and recall (6).

As it has been shown that rapid administration of fentanyl at a rate of 50 μg/kg in 60 seconds is associated with minimal hemodynamic alterations (7), we decided to administer 20 to 30 ml of undiluted fentanyl as a bolus dose into the venous infusion to deepen the anesthesia in unparalyzed patients. This resulted in convulsions in all five patients in whom this was done.

All narcotics, when administered in large enough doses, produce severe convulsions (8). The ED_{50} of intravenous fentanyl for deep surgical anesthesia in dogs is 0.025 mg/kg ($ED_{50\,dsa}$). The ED_{50} dose that produces severe convulsions is 4 mg/kg ($ED_{50\,sc}$) (8). From these two two values, a security index has been proposed, $ED_{50}\,sc/ED_{50\,dsa}$. The safety margin between the anesthetic dose and convulsive dose increases with increase in security index number. For fentanyl, the security index is 160 in dogs. However, in the canine experiments in which the security index was found to be 160, the fentanyl (4 mg/kg) was given slowly; the plasma value of fentanyl that produces convulsions was not determined.

During pharmacokinetic studies of fentanyl, rapid intravenous administration of 30 μg/kg of fentanyl to anesthetized and paralyzed patients resulted in a plasma fentanyl concentration of 320 ng/ml in 30 seconds (9). However, in one of our patients weighing 58 kg, slow intravenous administration of 25 ml of fentanyl (50 μg/ml) followed by a bolus of 30 ml of intravenous fentanyl (also 50 μg/ml) resulted in a

plasma concentration of 620 ng/ml and the onset of convulsions. Probably similar plasma fentanyl levels were achieved in the other four patients who also developed seizures.

All five patients had 10 mg of oral diazepam approximately 1 hour before induction of anesthesia. Two of these five patients, in addition to diazepam, also received 2 mg of lorazepam intravenously before the induction of anesthesia. Thus, oral pretreatment with diazepam and/or intravenous lorazepam may not inhibit or prevent convulsions produced by high plasma fentanyl levels.

In conclusion, rapid intravenous administration of fentanyl to provide rapid loss of conciousness, although not associated with significant hemodynamic changes, may produce convulsions that may not be attenuated with premedicant doses of diazepam or lorazepam.

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Lumbar Epidural Anesthesia in a Patient with Multiple Sclerosis

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Although spinal anesthesia has been implicated in postoperative exacerbation of multiple sclerosis (1, 2), no adverse effects have been reported in the relatively few patients in whom epidural anesthesia has been used (2, 3). The following is a case report of a patient with multiple sclerosis in whom a lumbar epidural block was performed on two separate occasions. Minor exacerbations of her disease state were noted following each epidural block.

Case Report

Anesthetic A. In 1977, a gravida 2, para 1, 21 year old was admitted in early labor with an intrauterine pregnancy of 32 weeks. Past history revealed that multiple sclerosis has been diagnosed in 1974. Signs and symptoms at the time of the original diagnosis were loss of bladder control, numbness in the thighs, and leg weakness. She was free of symptoms during her pregnancy and had no neurologic complaints or abnormal neurologic findings when she was seen in labor. She was afebrile at admission and throughout her peripartum course. During the period of active labor, a lumbar epidural catheter was inserted at the L2-3 interspace. A 2-ml test dose of 0.5% bupivacaine was administered, followed at 5 minutes by 8 ml of 3% 2-chloroprocaine, which resulted in analgesia extending from T-10 to S-5. Rapid progression of labor occurred, and a 32-weeks' gestation fetus was delivered vaginally 30 minutes later. One hour after delivery, the block had completely resolved. Eighteen hours later, she noticed an area of numbness on her inner right thigh. On examination, the only neurologic abnormality was a 10 cm x 15 cm area of hypesthesia on the medial aspect of her right thigh. Over the next 3 days

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the area became anesthetic and enlarged to include the entire medial thigh from the groin to just above the knee. Over the next 7 days she had gradual and complete return of sensory function.

Anesthetic B. In 1981 the same patient was admitted in premature labor with an intrauterine pregnancy of 28 weeks. Past obstetric history was significant for vaginal delivery in 1979 of a fetus of 23 weeks' gestation which later died of respiratory failure. No anesthesia was administered. Neurologic history since 1977 was positive for occasional episodes of right thigh numbness lasting 1 to 2 months. The most recent episode occurred during the fourth gestational month and lasted 6 weeks. At the time of this admission she was free of symptoms and without any discernible neurologic deficit. Labor could not be inhibited with terbutaline and so pelvic delivery was anticipated. She was afebrile and had been so throughout her peripartum course. A lumbar epidural catheter was easily inserted at the L3-4 interspace. A total of 55 ml of 0.5% bupivacaine was administered for pain relief during the next 9 hours. The catheter eventually became displaced, and another was inserted at the L2-3 interspace. Over the next 5 hours, a total of 26 ml of 0.5% bupivacaine was administered. At this time, a breech presentation was confirmed and a cesarean delivery was planned. A T-6 sensory level was achieved with 21 ml of 0.75% bupivacaine. Following delivery, general anesthesia was induced with thiopental and succinylcholine due to persistent discomfort and apprehension. Nitrous oxide, morphine, and diazepam were used for maintenance of anesthesia. In the recovery room the patient noted tingling in her inner right thigh; she still had significant motor blockade in both lower extremities. The motor block completely disappeared, but the tingling persisted. When examined 12 hours after delivery, she had an area of hypesthesia on her inner right thigh, which was similar in distribution to the area affected in 1977. The rest of her neurologic examination was normal. The area never became anesthetic. The numbness and tingling persisted for 7 weeks, after which complete sensory function returned.

Discussion

Multiple sclerosis is a demyelinating disease of the brain and spinal cord which is characterized by exacerbations and remissions over 20 or more years. Various factors, such as infection, emotional trauma, injury, and pregnancy are associated with relapses (4). More than half of the relapses associated with pregnancy occur in the postpartum period (5). This may be related to emotional and/or physical exhaustion (6).

Surgery and general anesthesia are also implicated in postoperative exacerbation of multiple sclerosis (7, 8). Baskett and Armstrong (8) suggested that barbi-

turates are associated with relapse of the disease. Other investigators, however, have failed to demonstrate such a relationship with barbiturates or any other general anesthetic agent (2, 9, 10). Hyperpyrexia, even of a minor degree, appears to be an important factor associated with exacerbation of multiple sclerosis in the perioperative period (9, 11).

The mechanism by which spinal anesthesia may exacerbate multiple sclerosis is unknown. Diagnostic lumbar puncture alone does not appear to induce relapses (12). Local anesthetic neurotoxicity, therefore, must be considered. Peripheral nerve blocks are not associated with exacerbations (2). However, the lack of a protective nerve sheath around the spinal cord and the associated demyelination may render the spinal cord more susceptible to the potential neurotoxic effects of local anesthetics. Recent reports (13) have suggested that chloroprocaine may be neurotoxic, and this agent was used on one occasion in this patient.

Epidural anesthesia may be less of a risk than spinal anesthesia, because the concentration of local anesthetic in the white matter of the spinal cord is 3 to 4 times higher following spinal as compared to epidural administration (1.37 μg/mg versus 0.4 μg/mg) (14, 15). Following multiple epidural reinforcement doses, however, the concentration of local anesthetic in the spinal cord may exceed some critical concentration. Signs of multiple sclerosis exacerbation might then occur.

The possible role of epidural anesthesia in the exacerbation of multiple sclerosis in this patient is not clear. On the first occasion the epidural anesthesia had completely resolved before the relapse. This suggests that the anesthetic might not have been responsible for the exacerbation. On the second occasion, a total of 562.5 mg of bupivacaine was administered over a period of 15 hours, and signs of altered sensation persisted for 7 weeks. This large dose of bupivacaine, administered extradurally, may have resulted in significant diffusion into the cerebrospinal fluid and into the spinal cord and may have exceeded some critical concentration above which neuronal

tissue is more susceptible to histotoxic responses to local anesthetics because of demyelination. On the other hand, other factors unassociated with bupivacaine cannot be ruled out.

In view of the known advantages of epidural anesthesia for labor and delivery, and as long as the patient is made aware of the risk/benefit factors and agrees to its use, there should be no absolute contraindication to the use of epidural anesthesia in patients with multiple sclerosis. This is especially true in the high risk pregnancy (e.g., prematurity, diabetes mellitus, cardiac disease) where epidural anesthesia is strongly indicated.

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letters
TO THE EDITOR

Duplication and Fragmentation in Publications

To the Editor:

Anesthesiology recently published an important study on the effects of epidural morphine by Bromage et al (1). To my great surprise I find the same study by the same authors published the same month in Anesthesia and Analgesia (2). The "Materials and Methods" and "Results" sections are nearly identical in the two papers (they should be as it is the same study). Different aspects are stressed in the two discussions. As the titles indicate, rostral spread of the epidural morphine is discussed in more detail in Anesthesiology, the nonrespiratory side effects in Anesthesia and Analgesia. Lengthening of the discussion by one page in one paper should make the other paper unnecessary.

The authors even (a) refer to the Anesthesiology paper in the Anesthesia and Analgesia paper, and (b) indicate that the respiratory side effects from the study are going to be published in a third (!) paper. The latter suggests unnecessary fragmentation of information, whereas the first two articles are not even that. Publishing the same morphine concentrations in a table in one journal and as a figure in the other does not make them different studies.

How can the authors defend the submission of the first two papers with the signed statement (which I assume they sent to both journals) declaring that the manuscript has not been submitted for publication in whole or in part elsewhere? Even a brief look at the two abstracts would cause one to question this. Is the need for a long publication list so important that such duplication (and frag-

mentation to follow) of otherwise good scientific material is warranted?

Following the precedent established by these authors, I submit this letter to the editors of both journals.

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To the Editor:

We are grateful for the opportunity to reply to Steen's allegations of deliberate duplication and fractionation of our morphine study.

Our earlier laboratory studies (1) with the more lipid-soluble narcotics, hydromorphone and methadone, had led us to some rather sanguine conclusions that could not be extrapolated to other agents with different physiochemical characteristics. These investigations on ourselves had given us first-hand insight into the behavior of methadone and hydromorphone, and we concluded that segmental spread was indeed limited. Even with high epidural administration at the first thoracic interspace, hypalgesia stopped at C-2 and did not extend into trigeminal territory. Side effects were minimal. None of us had difficulty passing urine after epidural administration, and CO_2-response curves were less depressed after epidural than after intravenous administration. In short, our findings fitted the hypothesis of limited segmental spread that most of us optimistically believed at that time.

At the outset of the subsequent morphine study (with approximately equianalgesic doses), it was immedi-

ately apparent that the pattern of events was dramatically different, quite complex, and urgently important from a clinical point of view. At the conclusion of the morphine study we were faced with a mass of data generated from more than 500 hours of direct observation and measurement. The material fell naturally into two parts, both of which contained unique and novel information that had been collected in a fashion that was not likely to be easily repeated by others because of the sheer rigor and discomfort demanded of both the volunteers and the observers. The first half of these data concerned rostral spread, and this seemed to be a new and complete story in itself. The side effects, which initially contained an incomplete summary of our respiratory data, formed a voluminous second half. Our observations and conclusions about the side effects were dramatically different from our own earlier conceptions, and in conflict with much of the published material available at that time. We believed, and still maintain, that all this new material was too extensive to compress into a single paper without losing much of its force and immediacy in the process. Unfortunately, our respiratory data were not fully reduced (and this work is still not fully processed at the time of writing), and the reviewer of our second paper requested that these incomplete respiratory data be either expanded or deleted. We felt the latter course was more prudent in view of the difficulties we were experiencing in agreeing on the correct statistical treatment of the respiratory material. Thus, the paper on side effects lost some of its most important content, and the final version was less complete than we had intended.

We appreciate and share Steen's concern about fragmentation and duplication of data, and most of us are aware of the insidious and widely

indulged temptations of the "LPU" or Least Publishable Unit, recently aired in *Science* (2). However, we can assure Steen that the two principal investigators of the papers in question are busy men, with better things to do with their limited time. In fact, events involving relocation of some of our research group have caused inordinate delays in publishing our complete respiratory findings. We hope that when this material is finally published Steen will have gained sufficient insight into the whole problem to be less judgmental.

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REFERENCES

1. Bromage PR, Camporesi E, Leslie J. Epidural narcotics in volunteers: sensitivity to pain and to carbon dioxide. Pain 1980;9:145–60.
2. Broad WJ. The publishing game: getting more for less. Science 1981;211:1137–9.

Experimental Hypoxia in Normal Patients

To the Editor:

In the recent paper by Knill et al (1), healthy, surgical patients were deliberately exposed to oxygen levels that were reduced so as to produce an end-tidal oxygen concentration of 6.5%. This corresponds to a PA_{O_2} value of roughly 45 torr which in the presence of even minimal venous admixture would yield a Pa_{O_2} value of approximately 40 torr.

This level of oxygenation is subnormal and, if not absolutely dangerous, is certainly associated with a reduced margin of safety which is inconsistent with optimal care.

Three issues are raised: First, why did the investigators feel it necessary to deliberately make anesthetized surgical patients hypoxemic? If it was

crucial to have this wide a range of Pa_{O_2} values for instrument calibration perhaps the authors themselves should have been the subjects for the lower oxygen concentrations. Second, how do you truly inform a lay person as to the physiologic reality of a Pa_{O_2} value of 40 torr, i.e., its meaning in terms of arterial and venous oxygen content, necessity for an increased cardiac output to maintain oxygen delivery, and the impact of anesthesia on the ability of the body to compensate? Third, what was behind the decision of the editorial board to publish results of such a study?

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REFERENCE

1. Knill RL, Clement JL, Kieraszewicz HT, Dodgson BG. Assessment of two noninvasive monitors of arterial oxygenation in anesthetized man. Anesth Analg 1982;61:582–6.

To the Editor:

The purpose of this research was to assess the accuracy and reliability of two noninvasive monitors of arterial oxygenation during inhalational anesthesia in humans. In evaluating the potential benefits and the potential risks of the hypoxic testing aspect of the study, my colleagues and I considered the following points:

1. Clinical signs of moderate hypoxemia seem unreliable during inhalation anesthesia, especially in the absence of visible freshly shed blood (1). We considered it important to assess the performance of instruments designed to monitor indices of arterial oxygenation continuously and noninvasively and to do so with subjects rendered briefly hypoxemic under controlled conditions.

2. The reliability of these instruments cannot be inferred from observations made in awake subjects, as anesthesia usually alters variables which in themselves can affect performance of these instruments, e.g., skin perfusion, blood pH, and skin temperature.

3. Controlled decreasing of arterial oxygen tensions has been practiced in physiologic and pharmacologic studies of human volunteers for many

years. Normal subjects have been rendered hypoxemic while awake, during natural sleep, while at altitude, during exercise, and while exposed to numerous drugs—including hypnotics and narcotics. The ventilatory response to hypoxemia is tested in many clinical pulmonary function laboratories. This considerable experience indicates that when hypoxemia (a) is induced progressively while controlling alveolar P_{CO_2}, (b) is monitored closely, and (c) is limited to the moderate level and the short duration used in our study (lowest P_{O_2} value maintained for less than 1 minute), there is virtually no risk of permanent adverse effect in healthy subjects studied in a wide variety of conditions. Indeed, lower oxygen tensions than those used in our study are necessary for hypoxic encephalographic changes to become evident and considerably lower tensions have been induced for much longer periods of time without apparent permanent complication (2–5).

4. Does inhalation anesthesia increase the risk of a brief period of moderate hypoxemia? Before this study, we had carefully induced moderate hypoxemia in approximately 70 anesthetized volunteers without detectable adverse effects (6–12). (It could be argued that on the basis of the effect of mild hypercarbia on the appearance of the hypoxic electroencephalogram (5), and the effects of halogenated anesthetics on cerebral blood flow and oxygen consumption, anesthesia in our subjects would increase the margin of safety. However, arguments of this nature are overly simplistic.)

The third and fourth points above represent the essential information given to potential volunteers concerning the "reality" of hypoxic testing. No attempt was made to speculate with volunteers about various oxygen tensions and contents and compensatory mechanisms. Subjects understood that they were participating in an experiment.

Assessment of the risk/benefit ratio of human research ultimately comes down to personal opinion. Such opinion should take into account all available relevant facts. In the case of research involving patients, assessments cannot be based merely on considerations of "optimal

(clinical) care," as research has its own particular risks and benefits. These principles, together with the above list of facts, may help to answer Saidman's queries.

Finally, the "golden rule" of ethnical human research was applied in this study. Before potential volunteers were approached, the undersigned was anesthetized and rendered hypoxemic several times—and more hypoxemic than the subjects of this study.

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Canada N6A 5C1

REFERENCES

1. Knill RL, Gelb AW. Peripheral chemoreceptors during anesthesia: Are the watchdogs sleeping? Anesthesiology 1982;57:151-2
2. Preswick G, Reivich M, Hill IP. The EEG effects of combined hyperventilation and hypoxia in normal subjects. Electroencephalogr Clin Neurophysiol 1965;11:56-64.
3. Shimojyo S, Scheinberg P, Kogure K, Reinmuth OM. The effects of graded hypoxia upon transient cerebral blood flow and oxygen consumption. Neurology 1968;18:127-33.
4. Cohen PJ, Alexander SC, Smith TC, Reivich M, Wollman H. Effects of hypoxia and normocarbia on cerebral blood flow and metabolism in conscious man. J Appl Physiol 1967;23:183-9.
5. Rebuck AS, Davis C, Longmire D, Upton ARM, Powles ACP. Arterial oxygenation and carbon dioxide tensions in the production of hypoxic electroencephalographic changes in man. Clin Sci Mol Med 1976;50:301-6.
6. Knill RL, Gelb AW. Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. Anesthesiology 1978;49:244-51.
7. Knill RL, Clement JL, Gelb AW. Ventilatory responses mediated by peripheral chemoreceptors in anaesthetized man. Adv Exp Med Biol 1978;99:67-77.
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11. Lam AM, Clement JL, Knill RL. Surgical stimulation does not enhance ventilatory chemoreflexes during enflurane anaesthesia in man. Can Anaesth Soc J 1980;27:22-8.
12. Knill RL, Clement JL. Variable effects of inhalational anaesthetics on the ventilatory response to hypoxaemia. Can Anaesth Soc J 1982;29:93-9.

The paper by Knill et al states that their study "was approved by the University of Western Ontario Committee on Human Research and each subject gave written informed consent." We do not subscribe to the hypothesis that editors have a special inside track to moral or ethical righteousness that permits them to veto the opinions of others, in this instance by members of a local committee in a well known and respected university. Editors have the right to disagree with decisions made on ethical or moral issues, but this is quite different than the right to impose their morality on others and thus interfere with another fundamental right: freedom of the press. —Ed.

book REVIEWS

The Clinical Core of Respiratory Medicine, by C. R. Woolf, Philadelphia, J. B. Lippincott Co., 1981, 304 pp, $18.50.

"Bad breath is better than no breath at all!" Using such common sense and humor, Dr. Woolf has provided students and housestaff with a useful and entertaining paperback manual of common pulmonary problems.

In the first of three parts, he describes his technique of obtaining a pulmonary-oriented history and physical examination and pertinent pulmonary function tests. His method of gathering and efficiently recording the history and examination concerning the five major pulmonary symptoms is a useful model for beginners. The author is a classifier who describes such matters as four grades of sputum according to the content of pus and five grades of dyspnea while walking.

The chapters on physical examination and reading a chest film relate his bedside teaching approach clearly. He describes both subtle but significant findings as well as classic but useless signs. Common sense abounds: Use only one viewbox per radiograph to avoid differences in illumination between each hemithorax.

The first part ends with a brief review of acute respiratory failure, including these four sound principles of therapy: oxygen is good; acidosis is bad; the only way to eliminate CO_2 is to breathe it out; and intermittent positive pressure ventilation or respiratory stimulants never cured anything.

Part 2 contains a chapter on each of the 16 most common reasons for obtaining a pulmonary consult in the author's hospital practice. Dr. Woolf

has a real knack for describing the several most typical presentations of an illness, plus the pitfalls in their evaluation. His sensible diagnostic and therapeutic approach is determined by the category of illness into which he places the patient. For instance, the management algorithm of the patient with a pneumothorax directs the reader through eight possible courses of action, depending on the amount of free air, the presence of air under tension, the number and site of previous pneumothoraces, the presence of severe chest disease, and any particular occupational hazard.

Part 3 has short chapters concerning the risks of operation with practical advice, medicolegal problems of compensation for occupational diseases, advice for the pregnant woman with chest disease, recommendations for patients aboard commercial aircraft, and restrictions for driving a motor vehicle.

This book makes the study of respiratory disease enjoyable and easy for students and residents otherwise beset by boring and heavy literature.

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Management of Medical Problems in Surgical Patients, edited by Mark E. Molitch, Philadelphia, F. A. Davis Co., 1982, 795 pp, $40.00.

There are many reasons for attempting to write a textbook in medicine. The avowed purpose of this textbook is to collate information that

is widely disseminated, yet perhaps not readily available. In addition, the book aims to provide information on the experiences of other internists, surgeons, and physicians who have had to deal with such patients, and the preface states that the text is designed with the medical consultant in mind. I believe that a medical consultant would already have well-in-hand the information presented in this book and therefore would have to refer to a more authoritative text if he wished to pursue a problem in depth. Unfortunately, I am afraid that what the authors have accomplished is what they initially stated they wished to avoid, that is, simply another large textbook of medicine.

An unfortunate problem in writing any textbook is that the book is frequently somewhat out of date prior to its publication; at least in some regard this text is no exception. A great deal of medical management of surgical patients is concerned with coronary artery disease and there is no mention of the new calcium channel antagonists and their effect on myocardial performance in this text.

Although the editor states that the opinions in this book are based on experience, I must take exception to many of the recommendations. The chapter on infectious disease recommends the use of prophylactic penicillin in burn patients. At least one study has shown this to result in increased severity of infection. The recommendation for anesthetic management of a patient with acute intermittent porphyria is a cyclopropane induction. I seriously doubt that most anesthesiologists would consider that to be the initial anesthetic management in these patients. In the section on pheochromocytomas, droperidol is mentioned as a good premedication. However, droperidol has been shown to induce hypertension in some patients with pheochromocytoma. These are two examples of rec-

ommendations, which are found throughout the text, by nonanesthesiologists for the anesthetic management of patients; this practice is of questionable benefit to the anesthesiologist.

This book has one extremely bright chapter, "Decision Analysis and Clinical Decision Making." As our ability to sustain life with artificial means increases, we as physicians are going to be faced with making some rather difficult decisions. The approach suggested by Dr Stephen G. Pauker is a valuable one.

In summary, this is indeed another large textbook of medicine that does not treat any one topic in a great deal of depth and would be useful primarily to medical students and surgical housestaff. It is not one I would purchase for my library.

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BOOKS RECEIVED

Managing Chronic Pain: A Patient's Guide, by C. D. Tollison, New York, Sterling Publishing Co, Inc, 1982, 144 pp, $10.95.

Obstetric Analgesia and Anesthesia, Volume 1, Current Reviews in Obstetrics & Gynaecology, by J. S. Crawford, New York, Churchill Livingstone Inc, 1982, 154 pp, $15.00.

Parenteral and Enteral Nutrition—A Practical Guide, by G. D. Phillips and C. L. Odgers, South Australia, GD Phillips and CL Odgers Flinders Medical Center, 1982, 310 pp, $13.75.

Acute Cardiovascular Management—Anesthesia and Intensive Care, by A. K. Ream and R. P. Fogdall, Philadelphia, Lippincott/Harper, 1982, 940 pp.

Respiratory Care Case Studies, by T. J. DeKornfeld and J. S. Finch, New York, Medical Examination Publishing Co, Inc, 1982, 288 pp, $20.00.

1982 Yearbook of Anesthesia, edited by R. D. Miller et al, Chicago, Year Book Medical Publishers, Inc, 1982, 295 pp.

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Annual Index

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   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

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Abbreviations. Define all abbreviations except those approved by the International System of Units for amount of substance, mass, length, time, temperature, electric current, and luminous intensity. Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

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THE WORLDWIDE CHOICE.

Over 500 million administrations throughout the world. Well over 125 million administrations in the United States alone.

Somewhere in the world—every two seconds—someone makes another decision to use FLUOTHANE® (halothane, U.S.P.). And for good reasons:

□ FLUOTHANE has been more widely investigated than any other inhalation anesthetic.

□ The FLUOTHANE experience shows association with hepatotoxicity to be extremely rare.[1] According to conclusions drawn from the United States National Halothane Study and other studies,* unexplained jaundice following anesthesia with halothane "...was a rare occurrence (approximately 1:30,000 administrations) and...the overall safety record of the anesthetic was excellent."[2]

□ FLUOTHANE "...is nearest to the ideal [inhalation anesthetic] presently available for children of all ages."[3]

□ FLUOTHANE has been recommended as the "anesthetic of choice"[4] for asthmatics.

□ And, of particular benefit in geriatrics and cardiovascular surgery: Excessive respiratory depression is rarely a problem with FLUOTHANE. Nor does it produce an increase in salivary or bronchial secretions.

*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., et al.: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

References:
1. Bunker, J.P., et al.: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology 43:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

Ayerst. Ayerst Laboratories
New York, N.Y. 10017

(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:

$$F-\overset{\displaystyle F}{\underset{\displaystyle F}{C}}-\overset{\displaystyle Br}{\underset{\displaystyle H}{C}}-Cl$$

The specific gravity is 1.872-1.877 at 20°C, and the boiling point (range) is 49°C – 51°C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20°C. The blood/gas coefficient is 2.5 at 37°C, and the olive oil/water coefficient is 220 at 37°C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), up to 0.00025% ammonia (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation.

FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

It has been reported that in genetically susceptible individuals, the use of general anesthetics and the muscle relaxant, succinylcholine, may trigger a syndrome known as malignant hyperthermic crisis. Monitoring temperature during surgery will aid in early recognition of this syndrome. Dantrolene sodium and supportive measures are generally indicated in the management of malignant hyperthermia.

Adverse Reactions. The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P., stabilized with 0.01% thymol (w/w), and up to 0.00025% ammonia (w/w).   **7197/R82**

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BRIEF SUMMARY
(Please consult package insert for full prescribing information.)

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED:
2 ml. ampuls—2 mg./ml.—boxes of 25, NDC #0052-0444-26
5 ml. ampuls—2 mg./ml.—boxes of 25, NDC #0052-0444-25
10 ml. vials—1 mg./ml.—boxes of 25, NDC #0052-0443-25

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The Ellis Fischel Cancer Center, recently designated a regional cancer center, is beginning a search for Director of Department of Anesthesiology. The Director would be expected to provide general and regional anesthesia for all types of cancer surgery. Experience in departmental administration is desirable. Experience in pain control and intensive care is desirable. Research and teaching opportunities are available. Salary is competitive with other institutions. Contact William G. Kraybill, M.D., Chairman of Search Committee for Anesthesiology, Ellis Fischel Cancer Center Hospital, Columbia, Missouri 65201. Phone: (314) 875-2214.

MARSHFIELD CLINIC

seeks anesthesiologist to join 7 M.D.s and 15 CRNAs in providing services for multispecialty group of 190 physicians and 512-bed referral hospital. Please send curriculum vitae to Sidney E. Johnson, M.D., Marshfield Clinic, Marshfield, WI 54449 or call collect at 715-387-5253.

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Board certification preferable, Arizona licensure, unique group practice, no OB, JCAH Hospital Accreditation—very early partnership. This position is available immediately. C.V. Reply to Box 11-82-B, c/o IARS.

PEDIATRIC ANESTHESIOLOGY RESIDENCY

Childrens Hospital of Los Angeles has advanced clinical program for residents at the second and third year level of training. Also accepting applications from practicing anesthesiologists who wish to update their knowledge and proficiency. Positions available from 2 months to 1 year. Specialized year approved by the AMA. For further details contact:
George B. Lewis, Jr., MD
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
4650 Sunset Boulevard
Los Angeles, CA 90027
Phone (213) 662-1708

WEST VIRGINIA UNIVERSITY:

Pain Clinic Fellowship commencing July 1, 1983 available to applicant with three years post graduate training in anesthesiology. Multi-disciplined Pain Clinic, seeing approximately 2,500 patients yearly, 25% of which are new patients. Clinic based on out-patient model with in-house beds available. Regular staff includes three anesthesiologists, a psychiatrist, and two clinical psychologists. Ancillary services include physical therapy, oral surgery and family practice. For further information contact Robert Bettinger, M.D., Director of Pain Clinic, Department of Anesthesiology, West Virginia University Medical Center, Morgantown, WV 26506. Deadline for applications is March 1, 1983. An equal opportunity/affirmative action employer.

ANESTHESIOLOGIST:

The Maryland Institute for Emergency Medical Services Systems has a need for anesthesiologists with an interest in trauma and critical care. The Institute is the clinical trauma center for Maryland statewide system. Opportunities for research, teaching and academic appointment available. Board certification preferred. Please contact: Peter Chodoff, M.D., M.P.H., MIEMSS, 22 S. Greene Street, Baltimore, Maryland 21201 (301) 528-3058.

ROCKY MTS./SOUTHWEST—

We have career and temporary positions available from solo to large group practice in the Rocky Mts. and Southwest. Expenses paid; partnerships usually available. Please contact Southwest Anesthesia Services, R.R. #9 Box 86 MM, Santa Fe, New Mexico 87501 (505) 983-7371.

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Department of Anesthesiology, Medical College of Ohio at Toledo, seeks qualified additional faculty at Assistant Professor and Associate Professor levels for clinical practice, teaching and research involvement. Adding high-risk obstetrical unit late 1983. Interest in regional anesthesia and pain management sought. Candidates must be ABA certified or eligible and have Ohio license. Competitive salary commensurate with background and experience. New medical school campus and hospital in attractive lake-side community with excellent family assets, and recreational opportunities. Please send letter, CV plus three references to John T. Martin, M.D., Professor and Chairman, Department of Anesthesiology, Medical College of Ohio at Toledo, CS 10008, Toledo, Ohio 43699.

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Anesthesiologist, Board certified or currently in the Examination System, interested in teaching, to join the Dept. of Anesthesia of the 950-bed Baystate Medical Center, Springfield, MA. Fee-for-service, P.C., Full share after one year. Please send C.V. or call: Franco Dinale, Chairman, or Howard Trachtenberg, V. Chairman, 759 Chestnut St., Springfield, MA. 01107 (413) 787-4327 or 787-4212.

OREGON:

Oregon Health Sciences University, Department of Anesthesiology is recruiting for faculty members at the Assistant and Associate Professor level. Specialized year training or equivalent experience desirable. Specific need exists in critical care, obstetrical anesthesia, pediatric anesthesia, and regional anesthesia and pain therapy although all applicants with strong clinical teaching ability and interest will be considered. Candidates must be eligible for Oregon Medical License. Please send C-V to Wendell C. Stevens, M.D., Oregon Health Sciences University, Department of Anesthesiology, 3181 S.W. Sam Jackson Park Road, Portland, OR, 97201. The Oregon Health Sciences University is an equal opportunity/affirmative action employer.

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Applications now being accepted for the 1983 academic year (early starting date available.) This is a 1-2 year program in a 24-bed multidisciplinary Critical Care Center with computerized cardiovascular monitoring, mass spectrometer and stat lab. In addition to clinical opportunities for research, investigation can be conducted in a well-equipped animal lab. Program affiliated with Jacksonville Health Education Program/University of Florida. Candidates must be Board eligible/certified in either anesthesiology, surgery or internal medicine. Send C.V. to: M. Mathru, M.D., Director, Critical Care Medicine, Memorial Hospital, P. O. Box 16325, Jacksonville, Florida 32216.

PEDIATRIC ANESTHESIOLOGY FEL-LOWSHIP—

The Children's Hospital, Denver, Colorado offers an approved PGY-4 fellowship year encompassing extensive operating room experience with opportunities for training in pediatric and neonatal intensive care, as well as participation in clinical research. 6,000 surgical procedures annually, 32-bed pediatric ICU and 32-unit neonatal tertiary care center. For information contact: Charles H. Lockhart, M.D., Director of Anesthesiology, The Children's Hospital, 1056 E. 19th Avenue, Denver, CO 80218.

OKLAHOMA:

Staff Anesthesiologist at Associate or Assistant Professor level to fill recently created staff position in general anesthesia. Must have completed a residency approved by the American Board of Anesthesiology. The person will be required to work with residents, interns and medical students in teaching and in the delivery of health care. Research interests are also desirable and facilities are available for those interested. Should be available 1982. Contact Bertram E. Sears, M.D., University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73190. Department of Anesthesiology Telephone: 405 271-4785 An equal opportunity employer.

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Staff Anesthesiologist at Associate or Assistant Professor level to augment existing staff of pediatric anesthesia at the Oklahoma Children's Memorial Hospital. Must be Board certified or qualified with interest in Pediatric Anesthesiology. Interest in working with residents, interns and medical students. Research opportunities available. An equal opportunity/affirmative action employer. Contact Bertram E. Sears, M.D., Department of Anesthesiology, University of Oklahoma, Oklahoma City, Oklahoma 73190 Telephone: (405) 271-4785

MARYLAND:

Opening for staff anesthesiologist. Minimal requirements are: 3 years residency training, experience in intensive care, neurosurgical, thoracic, obstetric and pediatric anesthesia, Board eligibility in Maryland, teaching interest. Clinical research interest desirable. Competitive stipend, outstanding fringe benefits. Full-time faculty appointment at The Johns Hopkins University School of Medicine. Send curriculum vitae to: T. Crawford McAslan, M.D., Chairman, Department of Anesthesiology, Baltimore City Hospitals, 4940 Eastern Avenue, Baltimore, Maryland 21224.

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Desire aggressive associate for physician administered anesthesia. Case load largely Cardiovascular and Thoracic. Free-for-service. Sunbelt. Send CV to Box 12-82-C, % IARS.

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(54)

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Now formulated without parabens, Regonol is a fast-acting reversal agent with documented advantages over neostigmine. It maintains greater cardiovascular stability,[1] causes fewer muscarinic side effects,[2] and has up to 33% longer action.[2] A wider margin between the anti-curare dose and the neuromuscular blocking dose[2] assures better control of the patient.

A step forward in reversal exclusively from Organon

25 mg in a 5 ml vial
(5 mg/ml)

References:[1]. Gyermek L: Curr Ther Res 18:377-386, 1975. **2.** Katz RL: Anesthesiology 28:528-534, 1967

BRIEF SUMMARY—(Please consult full package insert, enclosed in every package, before using Regonol)

INDICATIONS—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

CONTRAINDICATIONS—Known hypersensitivity to anticholinesterase agents: intestinal and urinary obstructions of mechanical type.

WARNINGS—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and antishock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly due to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those of the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg.) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia are thereby minimized. Reversal dosages range from 0.1-0.25 mg./kg. Usually 10 or 20 mg of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g. in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

HOW SUPPLIED—Regonol is available in:
5 mg./ml.: 2 ml. ampuls—boxes of 25—NDC-0052-0460-02
5 ml. vials—boxes of 25—NDC-0052-0460-05

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